ABSTRACTS OF WORLD MEDICINE

VOL. 17 NO. 2 FEBRUARY, 1955

Pathology

EXPERIMENTAL PATHOLOGY

292. **The Dormant Cancer Cell**
G. HADFIELD. *British Medical Journal* [*Brit. med. J.*] 2, 607–610, Sept. 11, 1954. 4 figs., 31 refs.

From a consideration of the extremely lengthy periods which sometimes occur between the excision of a primary tumour and the development of recurrent growths the author develops the concept of "temporary mitotic arrest" and discusses it in relation to the anatomical sites at which recurrences are found. As a possible source of information regarding the environmental factors which induce such mitotic arrest, experimental observations on the preservation of animal tumours at very low temperatures are surveyed and the suggestion is made that the "paramorphic" cells of Craigie may be related to, or identified with, the dormant cancer cells found in human pathology. *G. Calcutt*

293. **The Localising Action of Fibrinous Exudates**
T. D. DAY. *British Journal of Experimental Pathology* [*Brit. J. exp. Path.*] 35, 315–321, Aug., 1954. 2 figs., 3 refs.

Fibrin is considered to play an important role in the localization of tissue damage by acting as a mechanical barrier in the lymphatics and tissue spaces. In this paper from the University of Leeds the author describes experiments which indicate that during the process of clotting, particles of fibrin of a macromolecular order of size are formed, and that these, by impacting in connective tissue, diminish its permeability and thus lead to the localization of an inflammatory process.

The author's methods are described. Connective tissue, obtained from human subjects at necropsy and from freshly killed mice, was drawn over one end of a glass tube; this was then immersed in various fluids and the rate of flow through the connective-tissue membrane measured by the time taken for the meniscus of fluid in the tube to pass between two marks 1 mm. apart. There was only slight reduction of the rate of flow (as compared with that of a solution of citrate) when the membrane was perfused with serum or filtered diluted plasma, but a considerable slowing occurred when perfusion was with plasma to which thrombin had been added and the clotting process delayed by mechanical agitation or dilution. This slowing was reversed when streptokinase was introduced into the tube.

In the absence of flow across the membrane, the formation of a dense clot within and around the membrane produced only a very slight diminution of its permeability. Particles of latex (spheres of a uniform diameter of 0·25 μ) suspended in a citrate solution were unable to pass through the membrane and had no slowing effect on the rate of flow, but a solution of the macromolecular substance dextran had a very considerable slowing effect. *A. Ackroyd*

294. **Squalene Feeding in Experimental Atherosclerosis**
D. KRITCHEVSKY, A. W. MOYER, W. C. TESAR, J. B. LOGAN, R. A. BROWN, and G. RICHMOND. *Circulation Research* [*Circulat. Res.*] 2, 340–343, July, 1954. 22 refs.

Rabbits maintained on a diet containing squalene showed an increase in liver weight and in liver non-saponifiable material, but no more atheroma than did controls. Addition of squalene to a cholesterol diet did not lessen the severity of the cholesterol-induced atherosclerosis. Endogenous cholesterol, as represented here by that synthesized from squalene, did not cause atherosclerosis; exogenous cholesterol did.—[Authors' summary.]

295. **An Improved Method for the Production of Tubercles in a Chamber in the Rabbit's Ear**
A. G. SANDERS, L. F. DODSON, and H. W. FLOREY. *British Journal of Experimental Pathology* [*Brit. J. exp. Path.*] 35, 331–337, Aug., 1954. 6 figs., 6 refs.

The authors describe three modifications to the transparent rabbit-ear chamber which they have introduced in their work at the Sir William Dunn School of Pathology, Oxford, so that tissue already established in the chamber can be infected with tubercle bacilli with very little trauma. (1) The diameter of the central table was reduced from 8 to 5 mm., and the "perspex" buffer separating the table from the coverslip (which determines the thickness of the tissue in the chamber) was cut in the form of a ring of perspex 0·5 mm. wide and 30 μ higher than the central table, parts of the ring being milled away to allow the new tissue to grow into the central area. (2) A silver or zirconium pin 0·5 to 0·6 mm. in diameter, with a small flange near its outer end for protecting the perspex base of the chamber during manipulations with the pin vice, was used to fill the hole in the central table which is necessary for the introduction of the tubercle bacilli; a pin of stainless steel had previously proved unsatisfactory. (3) Zirconium bolts, sufficiently long to hold thin perspex covers in place on each side of the chamber in the intervals between examinations, were used instead of separate

splints and protective shields as formerly; these bolts are readily detachable and are sterilizable.

Sepsis was almost completely abolished by giving the rabbit a daily dose of 200,000 units of penicillin intramuscularly and by applying 1 in 1,000 acriflavine in a thick solution of gum tragacanth around the chamber after the operation. For inoculation of the tissue with tubercle bacilli the ear with the chamber was fixed in a suitable position to a special superstage fitted to the movable stage of the microscope, the zirconium pin described above was withdrawn fairly rapidly by means of a pin vice inserted into the microscope in place of an objective, and any dried serum scraped away from its shank. The end of the pin was then dipped into a drop of a culture of tubercle bacilli in Dubos–Davis medium, and after the drop had dried the pin was lowered into the hole in the central table until the flange was about 0·5 mm. above the base of the chamber; finally, water-soluble glue was run round under the flange and the pin pushed home. [The line drawings which accompany this paper make these modifications clearer than can any description in words.] *A. Ackroyd*

296. **Observations on Tuberculous Lesions in a Transparent Chamber in the Rabbit's Ear**
L. F. Dodson, A. G. Sanders, and H. W. Florey. *British Journal of Experimental Pathology* [*Brit. J. exp. Path.*] **35**, 338–344, Aug., 1954. 8 figs., 14 refs.

The authors describe the development of tuberculosis in a transparent chamber in the rabbit's ear after the introduction of bovine tubercle bacilli by the method described above [see Abstract 295]. The first inflammatory reaction attributable to the tubercle bacilli was recognized, on the average, 10 days after the inoculation of the newly formed tissue. The earliest stage of the formation of a tubercle was seen as a collection of 15 to 20 polymorphonuclear leucocytes in the interstitial tissue between capillaries. During the next 2 days their number increased several-fold and a few macrophages were also present. The latter enlarged and became more numerous while the number of polymorphs decreased, and debris was seen in the central area of the tiny tubercles which were now just visible at a magnification of $\times 16$. Reliable criteria could not be established by which the epithelioid cells seen in fixed, stained tuberculous tissue could be distinguished from these macrophages. As well as this type of cell, smaller cells intermediate in appearance between monocytes and epithelioid cells were present in the tubercle. Histiocytes, stained by a vital dye before the tissue was infected, did not migrate towards the developing tubercle.

Between adjacent foci a diffuse cellular infiltration, richer in polymorphs than the tubercle proper, soon appeared. By the 4th to the 7th day stasis, which was progressive, occurred in some of the blood vessels running through the lesion, and these soon became occluded; it was preceded by the adhesion of leucocytes to the endothelium of the affected vessels and was accompanied by local oedema. Necrosis increased as the stasis developed, and early in the 2nd week a fully developed tubercle was present. A tubercle did not expand at a uniform rate around its entire circumference, but grew intermittently at different sections of the edge as stasis and disintegration of blood vessels occurred. By the processes of stasis and thrombosis, accumulation of fresh cells at the margin of the growing tubercle, and extension of the caseous zone the whole of the tissue in the chamber was eventually converted into a caseous mass.

Although tuberculin hypersensitivity—which was considered to be present when a focal reaction occurred around a tubercle following an intravenous injection of purified protein derivative—may be responsible for some of the spontaneous events that can be seen in an infected chamber, it did not appear to be a necessary condition for the occurrence of necrosis, caseation, and vascular damage. When azovan (Evans) blue was injected intravenously it was observed to emerge from the blood stream in the area of a tubercle in its earliest stage of formation, and to be taken up by histiocytes, monocytes, macrophages, and epithelioid cells; if, however, the dye was injected when a mature tubercle with a caseous centre was present, it was not possible to detect it microscopically in the caseous material. The connective tissue in both an early tubercle and at the margin of a mature lesion was stained with the dye. *A. Ackroyd*

297. **Development of Acute Pulmonary Edema in Mice and Rats and an Interpretation**
B. Cassen and K. Kistler. *American Journal of Physiology* [*Amer. J. Physiol.*] **178**, 49–52, July, 1954. 1 fig., 4 refs.

298. **Effects of Preadministering Various Drugs on the Acute Pulmonary Edema Produced by Blast Injury and by the Intravenous Injection of Epinephrine**
B. Cassen and K. Kistler. *American Journal of Physiology* [*Amer. J. Physiol.*] **178**, 53–57, July, 1954. 2 figs., 5 refs.

In these two papers the authors' previous experimental findings (*J. Aviat. Med.*, 1950, **21**, 38 and 1952, 23, 115 and 120) are summarized and further original work, carried out at the University of California, Los Angeles, reported. In mice it was shown that the development of pulmonary oedema, as measured by changes in wet lung weight, occurs almost immediately after exposure to air blast or after the intravenous injection of massive doses of adrenaline, and it is therefore postulated that the mechanism is different from that involved in the more slowly developing pulmonary oedema of heart failure, the acute type probably being mediated through the central nervous system.

The previous administration of cholinergic drugs such as the choline esters to animals exposed to blast reduced the amount of pulmonary oedema, and this effect was not reduced by vagotomy. On the other hand adrenergic blocking agents did not protect against the induction of pulmonary oedema by blast, although they did protect against its induction by adrenaline. (The drugs were usually administered intraperitoneally, 3 to 30 minutes before exposure to blast or administration of adrenaline.) A better protective effect was obtained, however, by subdural injection, particularly in the case of acetylcholine. On the basis of these findings it is suggested that the

pulmonary oedema of blast is the result of hypothalamic shock and is mediated through the sympathetic nervous system, sudden closure of a large proportion of the pulmonary precapillary vessels causing a great increase in pressure in the capillaries which remain patent.

J. Naish

299. **The Trabecular Anatomy of Late Stages of Experimental Dietary Cirrhosis; its Pathogenesis in Terms of Rappaport's Structural Unit**

W. S. HARTROFT. *Anatomical Record* [*Anat. Rec.*] **119**, 71–93, May, 1954. 7 figs., 12 refs.

The development of fibrosis in the fatty livers of rats given a diet deficient in choline was studied at the University of Toronto. Thick, cleared sections of liver were injected with indian ink and then examined with the binocular dissecting microscope, when a 3-dimensional visualization of the vascular architecture was obtained. More conventionally stained frozen sections were also examined. The author's observations indicated that apparent anomalies in the distribution of fibrous tissue can be explained in terms of Rappaport's structural units [see Abstract 388]. Fibrosis was essentially non-portal in nature, and maximum tissue damage and fibrosis occurred at the periphery of these units.

P. C. Reynell

300. **Studies Concerning the Role of the Adrenal Cortex in the Pathologic Physiology of Diabetic Acidosis. I. Temporal Relations between the Metabolic Events of Experimental Diabetic Acidosis and the Level of Adrenal Cortical Function**

J. W. MCARTHUR, G. A. SMART, E. A. MACLACHLAN, M. L. TERRY, D. HARTING, E. GAUTIER, A. GODLEY, K. A. SWALLOW, F. A. SIMEONE, A. ZYGMUNTOWICZ, E. CHRISTO, J. CREPEAUX, W. W. POINT, and J. A. BENSON. *Journal of Clinical Investigation* [*J. clin. Invest.*] **33**, 420–436, March, 1954. 3 figs., 44 refs.

The authors describe an investigation carried out at the Massachusetts General Hospital (Harvard Medical School), Boston, into the role of the adrenal cortex in diabetic acidosis. For the purposes of the study 3 mongrel bitches were rendered diabetic by total pancreatectomy several months previously, and during the interval they were gradually accustomed to the experimental procedures in order to minimize the effects of any stress caused by these, a constant and strictly controlled diet was given, and the diabetes carefully stabilized with insulin. During the experiment itself metabolic balances over 12-hour periods were carried out before and during the withdrawal of insulin. In addition to measuring the metabolic balance of a large number of nutrients, the blood levels of many metabolites were determined and observations were made on the number of circulating neutrophil and eosinophil leucocytes and lymphocytes and on urinary corticosteroid excretion. In separate, modified experiments the insulin sensitivity of the animals at various times after insulin withdrawal was also estimated. The results of all these procedures are presented for each animal in a number of tables and graphs

It was found that a marked increase in adrenocortical function, as shown by the appearance of eosinopenia and increased corticosteroid excretion, was a comparatively late feature of the acidosis which followed insulin withdrawal, and was associated with the rather abrupt onset of a rapid deterioration in the state of the animals. This increased adrenal activity seemed also to be closely related in time to an increase in the breakdown of nitrogenous tissue, to a loss of potassium considerably in excess of that to be expected as a result of this breakdown, and to a decrease in insulin sensitivity. An increase in lipaemia and ketonaemia was also observed, but the temporal relationship of these metabolic events to adrenocortical hyperactivity was less clear.

G. A. Smart

301. **Studies Concerning the Role of the Adrenal Cortex in the Pathologic Physiology of Diabetic Acidosis. II. The Identification of Adrenal-conditioned Factors in the Physiologic Reaction to the Stress of Insulin Deprivation**

J. W. MCARTHUR, E. GAUTIER, K. A. SWALLOW, A. GODLEY, E. A. MACLACHLAN, M. L. TERRY, D. HUME, J. CREPEAUX, F. A. SIMEONE, H. KEITEL, and H. BERMAN. *Journal of Clinical Investigation* [*J. clin. Invest.*] **33**, 437–451, March, 1954. 3 figs., 34 refs.

The second part of this study of the role of the adrenal cortex in diabetic ketosis [see Abstract 300] was designed to demonstrate whether or not the metabolic changes previously observed were due to the adrenocortical over-activity. For this purpose the same observations as in the first part of the investigation were made and compared with the findings in a pancreatectomized dog during a 36-hour period of insulin withdrawal in the course of which ACTH (corticotrophin) was administered for 12 hours, and in a pancreatectomized, adrenalectomized dog maintained on a constant dose of cortisone and deoxycortone acetate both before and after the withdrawal of insulin.

The results in the 2 dogs showed interesting differences. In the pancreatectomized dog the administration of ACTH produced a striking acceleration of the animal's rate of progress towards diabetic acidosis. Polyuria was marked, vomiting began prematurely, and after only 36 hours of insulin deprivation the dog was moribund. The finding that ACTH increased ketosis in the pancreatectomized but otherwise intact animal seemed to suggest that ketosis is adrenally conditioned, but this was not borne out by the experiment on the adrenalectomized, depancreatized dog, in which the level of blood ketones did not differ materially from that previously observed in the pancreatectomized dogs.

From the results of these experiments it would seem that increased adrenal activity is of little or no significance in the genesis of ketonaemia. But, the authors conclude, " it would appear that the increase in adrenal cortical activity which occurs in response to the stress of insulin deprivation, by conditioning or sustaining a number of the other constituents of the alarm reaction to this stress, contributes significantly to the pathologic physiology of experimental diabetic acidosis ".

G. A. Smart

HAEMATOLOGY

302. **The Presence of A and B Antigens in the Platelets.** (Présence des antigènes A et B dans les plaquettes)
P. MOUREAU and A. ANDRÉ. *Vox Sanguinis* [*Vox Sang. (Amst.)*] **4**, 46–51, April, 1954. 4 refs.

Agglutination tests are difficult to carry out with platelets because of their tendency to agglutinate spontaneously. The authors, working at the Blood Transfusion Centre of the University of Liège, avoided these difficulties by absorbing anti-A and anti-B agglutinins with platelets from all four blood groups and testing the sera after absorption. They demonstrated that when A or B antigens were present in the erythrocytes they were also present in the platelets.

It is thought that the antigen lies within the platelet and not on its surface, little absorption occurring with suspensions of intact platelets. *I. Dunsford*

303. **Polyagglutinability of Red Cells.** [In English]
F. STRATTON. *Vox Sanguinis* [*Vox Sang. (Amst.)*] **4**, 58–65, April, 1954. 8 refs.

Polyagglutinability of erythrocytes is a comparatively rare phenomenon, only 12 cases having been reported hitherto, to which the present author now adds 6 more. Three of the new cases were in healthy blood donors and the others in patients suffering from haematemesis, peritonitis, and common cold respectively. The serological reactions in each case are given, and stress is laid on the importance of polyagglutinability as a source of false positive reactions during ABO grouping and of difficulty in the diagnosis of rare sub-groups such as A_4. *I. Dunsford*

CHEMICAL PATHOLOGY

304. **Level of C-Reactive Protein as a Measure of Acute Myocardial Infarction**
I. G. KROOP and N. H. SHACKMAN. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol. (N.Y.)*] **86**, 95–97, May, 1954. 1 fig., 13 refs.

The C-reactive protein (CRP) found in certain conditions in human serum is so called because it forms a precipitate with the somatic C-polysaccharide of the pneumococcus. It is probably an alpha globulin which is formed in response to an inflammatory reaction. Small amounts can be detected by a precipitin test, using an antiserum from rabbits hyperimmunized against purified CRP. At the Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, New York, the authors have examined the possible use of this precipitin test to differentiate those cases of coronary occlusion with myocardial necrosis and inflammation from those without inflammatory response. Tests on sera from 7 patients belonging to the first group, as shown by the presence of other signs of inflammation, all gave positive results, whereas those on sera from 6 patients belonging to the second group were all negative. *H. Lehmann*

305. **The Urinary Excretion of Calcium and Magnesium in Healthy Subjects and in Patients with Cancer.** (Calcium/Magnesium-Ausscheidung im Urin von Gesunden und Krebskranken)
A. STRIEBEL and H. BAUR. *Schweizerische medizinische Wochenschrift* [*Schweiz. med. Wschr.*] **84**, 1082–1085, Sept. 18, 1954. 3 figs., 26 refs.

The daily urinary excretion of calcium and magnesium was measured at the University Medical Clinic, Basle, in 100 healthy individuals, in 1,250 patients with diseases other than cancer, and in 115 patients with cancer. In the healthy group the ratios between Ca and Mg excretion, each measured in milliequivalents, in the various individuals were distributed along a Gaussian curve, in the group of patients without cancer the curve was flattened, and in the group with cancer the distribution was quite abnormal.

	No.	Ca:Mg Ratio		
		0·1–0·7	0·8–1·2	1·3–5·0
Healthy controls ..	100	21%	50%	29%
Patients with non-malignant diseases	1,250	39%	31%	30%
Patients with cancer	115	42%	8%	50%

The excretion of magnesium seemed to be constant in all groups, the differences in the Ca:Mg ratio being due to changes in calcium excretion. *H. Lehmann*

MORBID ANATOMY

306. **Encapsulated Angioinvasive Carcinoma (Angioinvasive Adenoma) of Thyroid Gland**
J. B. HAZARD and R. KENYON. *American Journal of Clinical Pathology* [*Amer. J. clin. Path.*] **24**, 755–766, July, 1954. 12 figs., 13 refs.

During the 30 years 1923–52 approximately 22,000 operations on the thyroid gland performed at the Cleveland Clinic, Ohio, yielded 2,500 encapsulated "adenomata", and 32 of these showed invasion of blood vessels. The patients included 19 women, their ages ranged from 11 to 66 years, and the tumour had been present for anything up to 51 years (average 9·6 years). Seven had been operated on within the past 3 years, 2 were not traced, and one had died of other causes; of the remaining 22 patients, 15 (68%) had had recurrences and 4 of these had died of the tumour. Metastases were chiefly in the bones, and none occurred in the cervical lymph nodes.

Angioinvasion is usually easily recognized histologically if a thorough examination of the capsular region is made. Artefacts produced by trauma are devoid of endothelium and their nuclei often distorted, while smooth, discrete islands of tumour cells lying within the substance of the capsule usually indicate angioinvasion. All but one of the tumours examined by the authors showed some indication of malignancy in histological detail, but it is emphasized that the presence of increased

cellularity, even of an atypical character, is a poor indication of prognosis in the absence of angioinvasion in this type of tumour. Among 57 encapsulated tumours showing cellular atypicality but no angioinvasion were 31 from patients who had been followed up for 5 to 28 years, in none of whom had there been any recurrence or metastasis. However, of tumours showing angioinvasion, a higher frequency of mitoses is found in those with a poor prognosis. *B. Lennox*

307. **Tumours of the Infantile Thymus.** (Über die Geschwülste des kindlichen Thymus)
H. S. BAAR. *Österreichische Zeitschrift für Kinderheilkunde und Kinderfürsorge* [*Ost. Z. Kinderheilk.*] **10**, 2–37, 1954. 18 figs., bibliography.

In this paper from Birmingham Children's Hospital the author records the findings in 6 cases of swelling of the thymus gland in children, of which 4 were cases of malignant tumour, one of benign growth, and one of epithelial cyst; in addition, the findings in a thymus gland removed on account of myasthenia gravis are described. The first of the cases of malignant tumour occurred in a boy of 11 months who died after a brief illness. At necropsy there was a well-delimited, firm, greyish-red growth measuring $7 \times 4 \times 1{\cdot}5$ cm., which had entirely replaced the thymus gland. Histologically it consisted of anaplastic epithelial cells with much amphophil cytoplasm, frequently displaying cytoplasmic projections incorporating islets of lymphoid tissue. Similar tumour growth infiltrated the thickened alveolar walls of the lungs and the periportal triangles in the liver. The second malignant case concerned a girl aged 3, who had started to limp in the right leg and developed a swelling over the right iliac crest with lymph-node enlargement on the right side of the neck and in the right axilla. She died, very emaciated, after a total illness of 6 months. Necropsy showed a well delimited, firm, pink growth, the size of an apple, stretching from above the manubrium sterni into the mediastinum; at its lower pole a rim of atrophic thymic tissue was still preserved. Paratracheal and posterior mediastinal lymph nodes were involved, and in the area of the right ilio-sacral joint there was a neoplastic ulcer which had destroyed much of the bone and had infiltrated deeply into the adjacent soft tissues. Microscopically, tumour tissue from all sites proved to be composed of large anaplastic cells with fair quantities of cytoplasm, sometimes displaying tumour giant-cells, while in some areas the cytoplasm was drawn out in protuberances like pseudopodia; fibrous-tissue bands divided the tumour into solid areas.

The third case was that of a girl of 2 years, who died after an illness lasting only 5 months. After a period of ill-defined complaints she became, one month before death, febrile and languid, developed facial cyanosis, venous engorgement of the anterior chest wall, spider haemangiomata of the sternal region, and an asymmetrical swelling of the anterior chest wall. Radiological examination of the chest revealed a shadow which was interpreted as a mediastinal tumour; at thoracotomy a decomposing tumour was found in the upper anterior mediastinum. The child died the same day. The post-mortem findings resembled those in the other cases. In addition, small tumour deposits were present in both lungs, the inferior vena cava was surrounded (though not invaded) by growth, and all tracheobronchial lymph nodes were affected. The fourth malignant case occurred in a boy aged 2 years and 10 months who was admitted on account of limping. Radiologically an extensive shadow in the right upper lobe was found. Later, a pleural effusion developed which was tapped repeatedly. Biopsy of a lymph node showed that the tissues had been almost entirely replaced by a cytoplasmic reticulum. Amongst the anaplastic cells were scattered small groups of lymphocytes, and occasionally a concentric arrangement was discernible, reminiscent of a Hassal body. Necropsy confirmed the presence of a primary carcinoma of the thymus, with extensive metastatic dissemination in the skeleton, liver, and lymph nodes in the axillae, neck, and body cavities.

The benign growth was observed in a boy of 9 years who was admitted on account of a painless swelling on the left side of the neck bordering on the upper pole of the left thyroid lobe. Histologically it consisted partly of normal thyroid tissue and partly of small cysts or nodules. There were many branching epithelial strands composed of large cells with foamy cytoplasm, occasionally forming epithelial multinucleated giant-cells. Xanthomatous degeneration was marked, and occasional stromal nodules consisted of masses of crystals, most probably cholesterin crystals. No recurrence was observed during the 4 years following removal of the growth. Lastly, a thymal cyst was discovered accidentally in a newborn infant who had died from bilateral adrenal haemorrhage. The cyst was filled with clear serous fluid and lined by a row of cuboidal or ciliated columnar cells. Although thymic tumours are rarely met with in juvenile myasthenia gravis, one such case is recorded. The patient was a boy of $3\frac{1}{2}$ years on whom a thymectomy was carried out successfully. The thymus gland weighed $36{\cdot}5$ g. and histologically was normal in structure, but numerous large reactive centres were found in the peripheral lymphoid tissue. The author compares his cases with similar cases described in the literature [and thus provides a most useful review]. *R. Salm*

308. **The Superficial Hidradenomata**
B. LENNOX. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **67**, 553–562, 1954. 5 figs., 16 refs.

The author divides the superficial hidradenomata into two groups. (1) The non-vulval superficial hidradenomata, which are intracystic papillary tumours of sweat ducts, in many cases of multicentric origin, consisting of fine, non-anastomosing papillae lined with a double layer of cells, a columnar luminal layer, and an inconspicuous basal layer of spheroidal cells. The papillae may have no stroma—the laciniate type of papilloma. The tumour may secrete a little mucin or develop some domed apocrine cells. Cilia are absent. Obstruction of the ducts may lead to dilatation, mucin retention, and apocrine metaplasia, destruction of the overlying skin leading to chronic inflammation, squamous replacement,

eversion, and ulcerative destruction. (2) Vulval superficial hidradenomata, consisting of one or more cysts filled with much-branched, freely anastomosing lamellae; the cells lining the lamellae are similar to those seen in the non-vulval tumours, and may show sub-apocrine change, never complete and never involving more than a quarter of the tumour. *C. L. Oakley*

309. **Xanthomatous Reticuloendotheliosis and its Relation to Leukaemia.** (Xanthomatose Retikuloendotheliose und ihre Beziehungen zur Leukämie)
P. FREUD and A. PLACHTA. *Österreichische Zeitschrift für Kinderheilkunde und Kinderfürsorge* [*Öst. Z. Kinderheilk.*] **10**, 57–70, 1954. 12 figs., 30 refs.

The authors describe a case seen at Flower and Fifth Avenue Hospitals, New York, which presented at first as a xanthomatous reticulosis, but later developed all the signs and symptoms of leukaemia. The patient, the son of Puerto Rican parents, was first seen in 1948 at the age of 11 months, when a diagnosis of juvenile xanthoma disseminatum was made and confirmed histologically. Six months later he was admitted to hospital with bronchitis, and at that time the leucocyte count was found to be 13,700 per c. mm., of which 71% were polymorphonuclear leucocytes and 25% were eosinophils. At the beginning of this fatal illness the serum cholesterol level was raised to 303 mg. per 100 ml., but soon fell to normal and remained so till the end. During the following 3 years there were many remissions and recurrences.

After less than 12 months' observation radiological examination of the lungs revealed diffuse miliary infiltrations, the first indication that the xanthomatous process was no longer confined to the skin. From early in 1949 onwards all varieties of primitive myeloid cell were regularly observed in the peripheral blood, the erythrocyte series, however, remaining at first unaffected. Gradually the leucocyte count rose to 141,000 per c. mm. In 1950 anaemia became pronounced, and enlargement of the liver and spleen was noticeable. Irradiation was successful only for a short time initially, but injections of urethane and later of triethylene melamine produced a long remission. From January, 1951, clinical deterioration was rapid. The boy became febrile, suffered from severe and repeated nose bleeding, petechiae of the skin, increasingly troublesome cough, vomiting, anorexia, and cachexia. The blood, apart from the anaemia, showed thrombocytopenia (60,000 per c. mm.) and very primitive myeloid cells numbering up to 231,000 per c. mm. Death occurred after attacks of dyspnoea and convulsions.

At necropsy the main findings were haemorrhages of the skin, mucosae, and serous membranes, gross hepato- and spleno-megaly, hyperplasia of bone marrow, xanthomata of skin, and atelectasis and bronchopneumonia. Microscopically, the architecture of the lymph nodes, marrow, spleen, and parts of the liver and other organs had been completely destroyed by a proliferation of a primitive, mononuclear, histiocytic type of cell, enmeshed in a fine reticulum network. Many of these cells were large, occasionally multinuclear, and displayed a foamy cytoplasm, in which much anisotropic lipid was demonstrable by polarized light. Chemical analysis showed that the cholesterol content of various organs was more than double the normal value, being increased to three times in the spleen and lymph nodes, and tenfold in the skin. All internal organs displayed evidence of extramedullary haematopoiesis. Inclusion bodies were present in all affected tissues, but were especially numerous in the lungs and adrenal glands. In the authors' opinion this finding might indicate an infective aetiology, but might also have been the result of a superadded virus infection.

Otherwise they interpret this case as one of primitive mesenchymal proliferation which had developed almost simultaneously in two directions, leading on the one hand to proliferation of primitive histiocytes and embryonal foam cells in the tissues, and on the other to myeloid leukaemic hyperplasia. As criteria for this newly observed type of reticulosis they suggest the following: (1) disseminated xanthomata of skin, with a normal serum cholesterol level; (2) generalized reticulosis of internal organs, with argentophil reticulum and foam cells and high cholesterol content of the tissues; (3) extramedullary haematopoiesis with primitive foam cells; and (4) a leukaemic picture in the blood and bone marrow and a fatal termination. *R. Salm*

310. **Giant-cell (Temporal) Arteritis**
R. H. HEPTINSTALL, K. A. PORTER, and H. BARKLEY. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **67**, 507–519, 1954. 4 figs. 37 refs.

The authors describe in detail 14 cases of temporal arteritis studied at St. Mary's Hospital, London, in 11 of which biopsy of the thickened vessels had been carried out, in 2 both biopsy and necropsy, and in one necropsy only. With the exception of one man of 48, the patients were all over 62 years old; 10 were men, 4 women.

In those coming to necropsy vascular lesions were extensive in the aorta, carotid arteries, and limb vessels, all showing much the same structure; the veins were unaffected. The intima was diffusely thickened, the inner part being mucinous, with many vacuoles, numerous, irregularly disposed, spindle-shaped cells, a few eosinophil leucocytes, and sometimes fine fibrosis, while the outer part showed less metachromatic material and far more cells—lymphocytes, histiocytes, and eosinophils, with occasional plasma cells and giant cells. Capillaries were numerous, and fine circular fibrosis common. In some cases there was a granular eosinophilic zone just internal to the internal elastic lamina, showing apparent fibrinoid degeneration and occasional deposits of haemosiderin. The internal elastic lamina showed extensive irregular destruction, with giant cells and histiocytes near the distorted remains. The media showed loss of many or all of its muscle fibres, with replacement or separation by large mononuclear cells and giant cells, usually of the Langhans type, sometimes arranged around granulomatous foci. Scattered plasma cells and polymorphonuclear and eosinophil leucocytes were often present; capillaries were common and fibrosis was present in 5 cases. The adventitia showed patchy or diffuse inflammatory changes, with

numerous lymphocytes and varying numbers of polymorphs, histiocytes, eosinophils, and plasma cells, with some fibrosis. No aneurysms were found. No acid-fast or other bacteria were demonstrated. The authors show that giant-cell arteritis has some resemblance to polyarteritis nodosa, but that it differs from that disease in being more common in the old, in the giant-cell reaction to the damaged internal elastic lamina, in its less rapid course, and in its predilection for peripheral arteries; in polyarteritis nodosa visceral arteries tend to be more frequently affected. *C.L. Oakley*

311. **A Contribution to the Study of the Pathogenic Mechanism of Bronchiectasis.** (Contribution à l'étude du mécanisme pathogénique des bronchectasies)
P. GALY and R. G. TOURAINE. *Lyon médical* [*Lyon méd.*] **192**, 49–59, July 18, 1954. 6 figs., 7 refs.

In this discussion, which emanates from Surgical Clinic A of the Faculty of Medicine, Lyons, the authors contend that infective hypostasis and inflammatory destruction of the bronchial or bronchiolar wall is a single pathogenetic mechanism occurring in all cases of bronchiectasis. This of course does not exclude the existence of other aetiological factors in bronchiectasis, nor does it deny the importance of contributory factors such as the presence of a foreign body or neoplasm, pleural adhesions, or congenital anomalies.

Evidence obtained by bronchography and from the macroscopical and histological examination of biopsy material indicates that the pathological course of events is dependent upon the anatomical site of the lesion. Thus involvement of the alveolar bronchioles ultimately results in fibrotic replacement and atelectatic changes rather than in ectasia; involvement immediately proximal to this site results in ectasia of cylindrical type, while involvement still higher up may result in saccular or fusiform bronchiectasis. In these changes at least two types of pathological process are concerned. (1) Most commonly there is a destructive panbronchitis which initially causes epithelial desquamation; this spreads into the bronchial wall, destroying the supporting-tissue elements, and so gives rise to dilatation. It is particularly marked in tuberculous bronchiectasis, where destruction and replacement fibrosis are ultimately so complete that no evidence of the specific causal lesion remains. (2) Alternatively, the bronchitis may be of subendothelial type. This spares the epithelium, but is no less destructive than panbronchitis, because the initial lympho-histiocytic nodules in the sub-endothelium spread to cause progressive destruction of the mural supporting-tissue elements.

When the alveolar bronchioles are involved, obliterative changes are initiated by the retention of secretions. While inflammatory changes are destroying the supporting-tissue elements, oedema and the formation of granulation tissue are simultaneously distorting the lumen. Ultimately all differentiation is lost and the bronchiole becomes totally replaced by fibrosis tissue. Involvement at a more proximal site results in dilatation rather than stenosis, this being brought about by a combination of such factors as retention of secretions, respiratory forces (especially if pleural adhesions are present), and by sclerotic and atelectatic changes in the adjacent lung parenchyma.

These observations lead the authors to the conclusion that bronchiectasis is induced by infective bronchitis in the presence of bronchial hypostasis caused by the severity of the infection or by pre-existing hypoventilation.
Adrian V. Adams

312. **Miliary Tuberculosis of the Bone Marrow. With Particular Reference to the Possibility of Diagnostic Aspiration Biopsy**
J. L. EMERY and N. M. GIBBS. *British Medical Journal* [*Brit. med. J.*] **2**, 842–843, Oct. 9, 1954. 11 refs.

To determine the value of bone-marrow aspiration biopsy in the clinical diagnosis of miliary tuberculosis specimens of sternal marrow from 44 children who had died from the disease were examined at Sheffield Children's Hospital (University of Sheffield). On the assumption that only 0·1 ml. of tissue can conveniently be aspirated during life, the amount of bone marrow examined in each case in the present investigation was restricted to 0·1 ml.

The case records showed that in 18 of the 44 cases miliary tuberculosis had been diagnosed clinically from examination of the retina and the radiological appearances of the chest. In the present investigation miliary tubercles were found in the bone marrow in 13 of the 44 cases, including 5 in which chest radiographs and examination of the retina had proved negative. Thus by means of bone-marrow biopsy a clinical diagnosis could have been reached in a further 5 cases.

It is concluded that bone-marrow aspiration biopsy is, theoretically, as useful a diagnostic procedure in miliary tuberculosis as *x*-ray examination of the chest or fundal examination, and that it is a reasonable procedure where miliary tuberculosis is suspected but not confirmed, especially if the cerebrospinal-fluid changes are equivocal. *J. B. Wilson*

313. **Frequency and Significance of Amyloid Changes in Rheumatoid Arthritis.** [In English]
G. TEILUM and A. LINDAHL. *Acta medica Scandinavica* [*Acta med. scand.*] **149**, 449–455, Aug. 17, 1954. 3 figs., 13 refs.

The incidence and significance of amyloid changes in rheumatoid arthritis was investigated at the University Institute of Pathological Anatomy, Copenhagen. Using methyl violet as a stain for sections of tissue obtained at necropsy in 28 cases of rheumatoid arthritis, the authors found amyloid deposits in 17, the amyloidosis being moderately severe or severe in 10. The deposits were most pronounced in the kidneys, spleen, and adrenal glands, but were also found in the liver, myocardium, and intestine. Vessel walls were frequently involved. Albuminuria was present in 13 of the 17 cases in which amyloidosis was found, and uraemia was the cause of death in 7 of the 28 cases. Amyloidosis was diagnosed clinically in only one case, and only in 2 was the condition recognized macroscopically at necropsy.
A. Wynn Williams

Bacteriology

314. **Serological Confirmation of Interstitial Pneumonia due to *Pneumocystis* in Infancy.** (Serologische Bestimmung der interstitiellen Pneumocysten-Pneumonie beim Säugling)
B. NAVRÁTIL, Z. ŠMÍD, and K. BÁRTA. *Annales paediatrici* [*Ann. paediat.* (*Basel*)] **183**, 59–64, July, 1954. 11 refs.

In a series of 66 cases of interstitial plasma-cell pneumonia in children seen at the Paediatric Clinic (Palacký University), Olomouc, Czechoslovakia, skin tests proved of no value as an aid to diagnosis. Satisfactory results, however, were obtained with a complement-fixation test. Acetone and alcohol extracts of dried lungs infected with *Pneumocystis carinii* were used as antigens and stabilized with an active lipid. The reaction was positive in all of 25 fatal cases in which the diagnosis was confirmed by histological examination. Among the 41 surviving patients a positive reaction was obtained in 30 cases and a negative reaction in 11. The antibodies appeared in the serum about 2 weeks after the first clinical symptoms and persisted for several weeks, or in some cases for several months.

H. S. Baar

315. **Investigation of Mycobacteria with the Neutral-red Test.** (Untersuchungen von Mykobakterien mit dem Neutralrottest)
H. HEIN. *Zeitschrift für Tuberkulose* [*Z. Tuberk.*] **103**, 339–343, 1953. (Received July, 1954.) 12 refs.

Working at the Institute of Hygiene and Microbiology, University of Würzburg, the author has subjected 123 strains of mycobacterium and 40 strains of other bacteria to the neutral-red test, and compared the results for some of the mycobacteria with their virulence in guinea-pigs. In carrying out the neutral-red test, bacteria grown in a solid medium (Hohne No. 4) or in Kirchner's synthetic serum medium are rubbed up in buffered saline and washed three times by centrifugation; the sediment is shaken vigorously with 50% methyl alcohol for one hour in a water-bath at 37° C., centrifuged, and again washed in alcohol. The sediment is then suspended in 5 ml. of veronal buffer at *p*H 8·9 and one drop of a concentrated aqueous solution of neutral red added; the mixture is shaken, allowed to stand for one hour and then centrifuged. The number of organisms used should be such that the supernatant remains yellow; avirulent mycobacteria are said to stain yellow, virulent ones different shades of red—the greater the virulence the deeper the red.

Five strains each of *Bacterium coli*, *Salmonella paratyphi* B, *Streptococcus pyogenes*, *Streptococcus* Type A, *Streptococcus* Type B, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Corynebacterium diphtheriae* all stained yellow, as did *Mycobacterium phlei* (6 strains), *Myco. smegmatis* (3), *Myco. thamnopheos* (3), *Myco. stercoris* (3), *Myco. lacticola* (5), and *Myco. tuberculosis* var. *hominis* H37Ra (1). Three strains of B.C.G. stained orange, one each of *Myco. marinum*, *ranae*, and *piscium* stained pink, and three of *Myco. friedmannii* red to red-violet. Of 79 strains of human tubercle bacilli, 4 stained yellow to clear brown, 16 pink, one (H37Rv) red, and 58 red to red-violet; of 14 bovine strains, 2 stained orange to pink, and 12 red to red-violet.

Two human strains of *Myco. tuberculosis* from each of the groups staining red, pink, and yellow were used to infect guinea-pigs; it was concluded that their virulence in guinea-pigs and in man ran parallel with their degree of red-staining as shown by the neutral-red test. The author suggests that yellow staining of mycobacteria in this test is due to the lipopolysaccharide present, and the red staining to mycholic acid. *C. L. Oakley*

316. **The Early Specific Protective Action of Tetanus Toxoid Given in Massive Doses.** (Action préventive spécifique précoce de l'anatoxine tétanique employée à doses massives)
E. LEMÉTAYER, M. RAYNAUD, L. NICOL, and A. TURPIN. *Annales de l'Institut Pasteur* [*Ann. Inst. Pasteur*] **87**, 1–24, July, 1954. 38 refs.

In experiments carried out at the Pasteur Institute, Garches, the authors showed that the injection of large doses of tetanus toxoid into mice and guinea-pigs specifically prevents or delays the local and general effects of tetanus toxin when this is injected subsequently, resistance developing almost at once after the intravenous injection of toxoid. If both toxoid and toxin are injected intramuscularly into the same limb, local and general resistance are demonstrable almost immediately; if the toxin is injected into the opposite limb, however, general resistance is present within 5 minutes, but local resistance develops only after 15 hours. In both cases the resistance begins to diminish within 24 to 48 hours and has disappeared by the 10th day. The blood of guinea-pigs taken one hour after the injection of 3,000 to 6,000 units of toxoid has marked neutralizing properties against the toxin, 1 ml. of the serum neutralizing 0·1 M.L.D. of toxin, but these also fall off rapidly and are completely absent by the time normal immunity has developed. A toxin-neutralizing substance can also be extracted from the muscles of protected guinea-pigs.

The authors suggest in explanation of their results that there is competition between toxoid and toxin for specific cellular receptors, large doses of toxoid saturating these sites and so preventing the fixation of toxin. On the other hand, the injection of massive doses of toxoid will not prevent a fatal outcome in established cases of tetanus, since it cannot displace the toxin from its attachment to the receptors. *M. Lubran*

Pharmacology

317. **The Effect of Morphine on Bronchial Muscle**
H. S. MITCHELL and J. D. DEJONG. *Journal of Allergy* [*J. Allergy*] **25**, 302–305, July, 1954. 2 figs., 13 refs.

In experiments performed at McGill University, Montreal, chains of bronchial rings from non-allergic human subjects and from dogs were exposed *in vitro* to morphine in a concentration of 10 mg. per 100 ml. This caused neither relaxation nor contraction. However, the contraction caused by acetylcholine was increased if morphine was added to the bath beforehand, although that caused by histamine was not potentiated by morphine. These findings, it is suggested, support the theory that the adverse effect of morphine in bronchial asthma may be due to its inhibitory effect on cholinesterase.

H. Herxheimer

318. **Pharmacological Studies with Rescinnamine, a New Alkaloid Isolated from *Rauwolfia serpentina***
G. CRONHEIM, W. BROWN, J. CAWTHORNE, M. I. TOEKES, and J. UNGARI. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol. (N.Y.)*] **86**, 120–124, May, 1954. 8 refs.

The root of *Rauwolfia serpentina* is known to contain alkaloids other than reserpine, and one of these, rescinnamine, which was recently isolated, has been studied pharmacologically by the authors. The drug was given to dogs in doses ranging from 1 μg. to 300 μg. per kg. body weight by mouth in capsules daily over 5 days, or intravenously in an acid solution at *p*H 3 to 5. At 20 hours after the intravenous injection or on the 6th day after oral administration the degree of sedation was estimated, using spontaneous activity and response to stimulation as criteria; the arterial pressure and heart rate were also recorded.

Diarrhoea and prominence of the nictitating membrane were frequently observed. Bradycardia, hypotension, and, at higher doses, sedation occurred. Between 3 and 4 hours after a single dose of 300 μg. per kg. the mean arterial pressure of dogs anaesthetized with pentobarbitone had dropped significantly and the primary pressor increase in response to central vagal stimulation had disappeared. With the same dose the response to bilateral carotid occlusion was less at the end of 7 hours than before the injection of the drug. This type of experiment did not demonstrate bradycardia. Rescinnamine also caused augmentation of the pressor rise in response to adrenaline.

In further experiments the sleeping time of mice given pentobarbitone was significantly prolonged after an intraperitoneal injection of 5 mg. of rescinnamine per kg. body weight, and voluntary motor activity was greatly reduced within one hour of injection. In doses of 2 mg. per kg. the drug caused ptosis, and an increase of the dose to 30 mg. per kg. resulted in complete closure of the eyes. In rats, a dose of 10 mg. per kg. produced marked sedation and a copious nasal discharge.

The authors conclude that on a weight basis, rescinnamine appears to be several times as potent as " rauwiloid " but of roughly similar potency to reserpine.

Norval Taylor

319. **Chlorpromazine. A Study of its Action on the Circulation in Man**
C. A. FOSTER, E. J. O'MULLANE, P. GASKELL, and H. C. CHURCHILL-DAVIDSON. *Lancet* [*Lancet*] **2**, 614–617, Sept. 25, 1954. 6 figs., 7 refs.

In a study of its effect on the human circulation chlorpromazine (dimethylaminopropyl-N-chlorophenothiazine hydrochloride; " largactil "), injected in doses of 5 to 50 mg. into the tubing of an intravenous infusion of saline or 5% dextrose, was administered to 10 conscious volunteers and to 12 anaesthetized patients at St. Thomas's Hospital, London.

The drug usually produced a fall in blood pressure and a rise in pulse rate, but these effects were variable and may have been related to the speed of injection and to the age of the subject. In the 10 conscious subjects there was marked vasodilatation in the limbs, especially in the hands. Further experiments with intra-arterial and intravenous infusions suggested that the vasodilator action on the hand was due to both central and local effects, particularly the former. The response to the cold constrictor test was greatly reduced by the presence of chlorpromazine in the general circulation. Chlorpromazine diminished the pressor effect of an intravenous injection of noradrenaline, bradycardia being replaced by tachycardia, and the drug given intravenously (but not when given intra-arterially) also reversed the action of adrenaline on the vessels of the hand—the first demonstration, the authors believe, of the reversal of the action of adrenaline by another drug. They therefore recommend the use of noradrenaline, rather than of adrenaline, to restore the blood pressure in cases of excessive hypotension due to chlorpromazine.

I. Ansell

320. **Phenylboric Acid and Anti-epileptic Activity.** (Acide phénylborique et activité antiépileptique)
F. CAUJOLLE, G. ROUX, and C. MOSCARELLA. *Bulletin de l'Académie nationale de médecine* [*Bull. Acad. nat. Méd. (Paris)*] **138**, 267–272, May 25, 1954. 12 refs.

The authors have previously shown that phenylboric acid enhances the effect of several different hypnotics, such as chloral and the barbiturates, even though it possesses no hypnotic properties itself.

In the present work, based on experiments performed on rats, they show that the intraperitoneal injection of 150 mg. of phenylboric acid per kg. body weight 40

minutes before the administration of 80 mg. of leptazol per kg. suppressed the typical epileptiform convulsions, producing instead a milder type of convulsion. The same dose of phenylboric acid, however, had only a feeble effect against convulsions induced by electric shock in rats. The effective dose of phenobarbitone necessary to inhibit the convulsive effect of leptazol could be reduced by 50% after the administration of phenylboric acid.

The authors conclude that phenylboric acid is not of much value as an anti-epileptic agent by itself, but that it is useful in combination with phenobarbitone and " phenurone " (phenacemide) in enhancing the effects of these substances. It is claimed that these effects have been confirmed in patients. *R. Wien*

321. **Evaluation of a New Analgesic**
S. C. HARRIS and R. C. WORLEY. *Journal of Applied Physiology* [*J. appl. Physiol.*] **7**, 84–88, July, 1954. 2 figs., 13 refs.

The pharmacology and effect on the pain threshold of a new analgesic, " daprisal ", which consists of a mixture of D-amphetamine, amylobarbitone, phenacetin, and aspirin, were studied at the Northwestern University Dental School, Chicago. Using the method of electrical stimulation of the tooth pulp the authors found that the analgesic raised the pain threshold significantly in 15 subjects, whereas a placebo, 32 mg. of codeine phosphate, and a compound containing codeine phosphate, caffeine, phenacetin, and aspirin were all without significant effect. Clinically daprisal was effective in patients with pain which was severe and likely to recur or persist, most of the patients preferring it to the compound.

[This pharmacological experiment, although valid and well-controlled, is of little value, since it does not indicate which is the active constituent of daprisal or, indeed, whether all the constituents are essential.]

Thomas B. Begg

322. **Drugs Preventing Motion Sickness at Sea**
S. W. HANDFORD, T. E. CONE, H. I. CHINN, and P. K. SMITH. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol.*] **111**, 447–453, Aug. 10, 1954. 1 fig., 10 refs.

Diphenhydramine hydrochloride (" benadryl "), scopolamine hydrobromide, and " postafene " (*p*-chlorobenzhydril-*m*-methyl benzyl ethylenediamine hydrochloride), which are known to be effective in preventing sea-sickness, were re-evaluated in order to determine the drug of choice and the dosage required to give maximum protection with minimum side-effects. The drugs were given to troops during a voyage from New York to Bremerhaven in the following dosages: diphenhydramine, 50 mg. three times a day; scopolamine, 1 mg. twice a day; postafene, 50 mg. once only at the time of sailing. A placebo was given to controls. Vomiting occurred in 34% of the controls, 13% of the subjects given diphenhydramine, 19% of these given postafene, and 33% of these given scopolamine. Diphenhydramine and postafene were significantly free from undesirable effects. Other drugs tested were chlorpromazine and a commercial preparation, No. 01780 ((3-chloro-5-benzyl)-phenyldimethylaminoethyl ether hydrochloride); the percentage of subjects who vomited after administration of these two drugs was 27 and 22 respectively. The action of the single dose of postafene lasted for about 24 hours. *V. J. Woolley*

323. **The Pharmacology of 1-*cyclo*Hexyl-1-phenyl-3-pyrrolidino-1-propanol Methsulfate, Compound 14045, a New Parasympathetic Depressant**
H. M. LEE, W. GIBSON, W. G. DINWIDDIE, and J. MILLS. *Journal of the American Pharmaceutical Association* [*J. Amer. pharm. Ass.*] **63**, 408–413, July, 1954. 4 figs., 20 refs.

324. **Bis-[β-(*o*-methoxyphenyl)*iso*propyl]-amine; Pharmacologic Studies of a New Local Anesthetic**
W. B. BASS, L. A. SCHROEDER, and M. J. VANDER BROOK. *Current Researches in Anesthesia and Analgesia* [*Curr. Res. Anesth.*] **33**, 234–242, July–Aug., 1954. 14 refs.

The local anaesthetic properties of bis-[β-(*o*-methoxyphenyl)*iso*propyl]-amine, or " U-0045 ", were unexpectedly discovered during the evaluation of a group of similar compounds for bronchodilator activity. It differs from other local anaesthetics in that it is a secondary amine containing neither ester nor amide linkage, and is consequently less susceptible to hydrolysis. Its solubility in water is 5%, but the maximum concentration possible in physiological saline is 0·05%, since higher concentrations result in precipitation of the hydrochloride salt. It is very soluble in alcohol.

As a surface anaesthetic U-0045 lactate was approximately 200 times more active than cocaine on the rabbit's cornea. When applied to abrasions and lacerations in guinea-pigs, 0·5% of U-0045 lactate in a " carbowax " ointment base produced analgesia lasting approximately 4 times as long as the same concentration of cyclomethycaine. For infiltration analgesia the guinea-pig intradermal weal test of Bullring and Wajda showed U-0045 lactate to be 40 to 50 times more active than procaine hydrochloride, while subcutaneous infiltration with 2 ml. of 0·02% solution gave sufficient analgesia in guinea-pigs for laparotomy to be performed, and infiltration with 5 ml. of a 0·05% solution permitted incision through the fatty layers of the abdominal wall in the dog. For spinal analgesia U-0045 lactate was 4 times more active than tetracaine hydrochloride in rabbits, and 2½ times more active in dogs. In the latter it was at least 50 times more active than procaine hydrochloride.

No evidence of irritation was produced by the rectal administration to rabbits of 1 g. of an ointment of 0·5% U-0045 in a petrolatum base twice daily for 10 days, or by application of 5 g. of this preparation twice daily for 2 weeks to extensive burns in rabbits. There were no signs of systemic activity and no retardation of healing rate when the same ointment was applied twice daily for 2 weeks to abrasions of the skin of rabbits.

It is concluded that U-0045 and its lactate can be safely and effectively employed for topical, infiltration, and spinal analgesia or anaesthesia in animals. Clinical trials are now in progress. *Robert Hodgkinson*

Chemotherapy

ANTIBIOTICS

325. **Staphylococci and Combinations of Antibiotics *in vitro*.** (Staphylocoques et associations antibiotiques *in vitro*)
R. DEBRÉ, M. PEYRE, H. VELU, and C. GERBEAUX. *Revue d'immunologie et de thérapie antimicrobienne* [*Rev. Immunol. (Paris)*] **18**, 113–119, 1954. 12 figs., 45 refs.

This article is something of a philosophical treatise on the complex subjects of synergism, antagonism, and the additive effects of different associations of antibiotics. It confirms to a large extent the views expressed by Jawetz *et al.* (*J. Bact.*, 1952, **64**, 29; *Abstracts of World Medicine*, 1953, **13**, 14) and by Gunnison and Jawetz (*J. Bact.*, 1953, **66**, 150), and is based on the authors' personal study of the effect on 4 strains of staphylococci of associations of (*a*) penicillin and streptomycin, (*b*) streptomycin and chloramphenicol, and (*c*) streptomycin and " terramycin " (oxytetracycline).

The results are expressed in a large number of figures and graphs [which are not easy to interpret], and the conclusions appear to be as follows. (1) The association of streptomycin and chloramphenicol was less effective than that of streptomycin and penicillin. (2) Additive effects were maximal when each antibiotic was used at its mean bacteriostatic or bactericidal concentration. (3) Antagonism was observed on only one occasion, namely, with a combination of chloramphenicol and streptomycin, and even so the antagonistic effect was only a feeble one.

The authors themselves admit that the interpretation of the results is difficult and their clinical significance even more doubtful, pointing out that in this type of experiment *in vitro* there are so many variable factors—such as size of the inoculum, differences in strains of test organism, composition and reaction of the medium, duration of the test, type of action of the agent tested (bacteriostatic or bactericidal)—that unless strictly standardized conditions of technique and design of experiment are enforced, then the significance and interpretation of results become a matter of conjecture. They quote [and obviously endorse] a remark made by Gunnison and Jawetz to the effect that it is not known which laboratory test coincides best with the chemotherapeutic effect in man—if indeed any relationship at all exists.

R. Wien

326. **Penicillin in Sesame Oil and Fibrosarcoma. A Report of Two Cases**
I. S. GOLDENBERG. *Cancer* [*Cancer (N.Y.)*] **7**, 905–909, Sept., 1954. 3 figs., 8 refs.

Two cases are reported of fibrosarcoma of the buttocks following injections of penicillin in sesame oil. A survey of the literature is presented regarding experimental studies of carcinogenicity of naturally occurring fats and oils. Attention is called to the fact that oil preparations of biologicals may not be completely innocuous.—[Author's summary.]

327. **Benethamine Penicillin: a New Salt with a Prolonged Action**
M. G. NELSON, J. M. TALBOT, and T. B. BINNS. *British Medical Journal* [*Brit. med. J.*] **2**, 339–341, Aug. 7, 1954. 2 figs., 4 refs.

The first clinical trials of a new penicillin compound, the N-benzyl-β-phenylethylamine salt (benethamine penicillin), are described. During these trials, which were carried out at three hospitals, some 120 intramuscular injections of benethamine penicillin were given. In 5 instances some local reaction occurred, but this was never severe; no general reactions were observed.

After a single injection of 300,000 to 900,000 units a bacteriostatic blood level of penicillin was maintained for 3 to 6 days, depending on the dose and the individual response. It is suggested that one or two injections should be adequate for the treatment of the more sensitive and accessible infections seen in general practice.

A. W. H. Foxell

328. **Variations in Antimicrobial Activity of the Tetracyclines**
H. WELCH, W. A. RANDALL, R. J. REEDY, and E. J. OSWALD. *Antibiotics and Chemotherapy* [*Antibiot. and Chemother.*] **4**, 741–745, July, 1954. 1 fig., 17 refs.

The authors first give an extensive review of previous clinical and laboratory reports in the literature of differences in the therapeutic activity of oxytetracycline (" terramycin ") and chlortetracycline (aureomycin), and suggest that similar clinical reports comparing these two substances with tetracycline itself are to be expected. Some laboratory evidence of this nature has already appeared; it has been shown, for example, that tetracycline is only one-quarter as effective as chlortetracycline in treating toxoplasmosis in mice.

They then present the results of sensitivity tests carried out at the U.S. Department of Health, Washington, D.C., on 338 strains of coagulase-positive staphylococci with the three tetracyclines, a plate-dilution technique being employed. Chlortetracycline was found to be considerably more active against more strains than the other two substances. Of the 215 strains sensitive to chlortetracycline in concentrations up to 0·78 μg. per ml., 149 (69%) were sensitive to concentrations of 0·39 μg. per ml. or less, whereas of 213 strains sensitive to 0·78 μg. of tetracycline per ml. or less, only 71 (33·3%) were sensitive at concentrations of 0·39 μg. per ml. or less. At concentrations of 0·78 μg. per ml. or less only 30 strains were sensitive to oxytetracycline. In regard to resistance, 49 strains (14·4%) were resistant to a concentration of 100 μg. per ml. or more of tetracycline,

55 (16·2%) to a similar concentration of oxytetracycline, while the number resistant to chlortetracycline was only 33 (9·7%).

The authors conclude that these findings suggest caution in regarding the three substances as having " equivalent antibacterial activity ", in spite of their very similar molecular structure. Although it is true that in general tetracycline produces fewer side-effects than its analogues, this may not be sufficient reason for its use in place of chlortetracycline or oxytetracycline.

Derek R. Wood

329. **Tetracycline: Studies on Absorption, Distribution, Excretion, and Clinical Trial in Children**

S. SCHWARZER, R. REEVES, A. CLAPS, and A. F. ANDERSON. *Journal of Pediatrics* [*J. Pediat.*] **45**, 285–292, Sept., 1954. 3 figs., 13 refs.

Tetracycline is absorbed rapidly into the blood stream after oral administration. Antibiotic activity was detected one half-hour after 25 to 50 mg. per kilogram doses. Therapeutic serum levels of 8 hours' duration were produced with a single 6 mg. per kilogram dose. Further increase of dosage produced a proportional increase of serum concentration. A marked cumulative effect was obtained by the second day of therapy, when the dose of 3 and 6 mg. per kilogram was given at 6-hour intervals, thereby providing more effective blood levels.

Tetracycline diffuses poorly into the cerebrospinal fluid in patients without meningeal inflammation. The spinal fluid level ranged from one-eighth to one-thirtieth of the simultaneously obtained serum levels. Tetracycline is excreted in high concentrations up to 1,000 μg. per ml. in the urine. The total excretion over a 24-hour period was 26·5% of the given dose.

Patients show a high tolerance to the drug. A remarkable lack of side reactions was observed even with a dose of 150 mg. per kilogram per day. Of 51 patients treated with the oral suspension, 84·5% were cured, 7·8% improved, and 1·9% unimproved. There were three (5·8%) recrudescenses. The studies indicate that the effective oral dose of tetracycline is 25 mg. per kilogram per day given at 6- to 8-hour intervals.—[Authors' summary.]

330. **The Synergistic Amebicidal Effect of Tetracycline, Oxytetracycline and Carbomycin on Cultures of *Endameba histolytica***

H. SENECA and E. BERGENDAHL. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **228**, 16–20, July, 1954. 9 refs.

The authors describe tests carried out *in vitro* at Columbia University, New York, on cultures of *Entamoeba histolytica* to determine the amoebicidal effect of the antibiotics tetracycline, oxytetracycline, and carbomycin, alone and in various combinations. Pure cultures of 3 strains of *E. histolytica* and monobacterial cultures with *Bacterium coli*, *Aerobacter aerogenes*, and *Clostridium perfringens* were grown in a diphasic medium consisting of an inspissated whole-egg slope covered with buffered saline and containing sterilized starch. Serial dilutions in saline of the antibiotics to be tested, giving concentrations ranging from 1,000 to 7·81 μg. per ml., were added in 5-ml. amounts to the tubes of medium, which were then inoculated with approximately 50,000 amoebae from 48-hour cultures and incubated for 48 hours. Microscopical examination of the cultures was carried out after 24 and 48 hours.

All 6 strains of *E. histolytica* were inhibited by oxytetracycline in concentrations of 31·25 to 250 μg. per ml. and by tetracycline in concentrations of 62·5 to 250 μg. per ml. The inhibitory effect was increased fourfold when tetracycline and oxytetracycline were used in combination, and twofold when either of these was combined with carbomycin.

C. A. Hoare

331. **Metabolic and Histologic Studies in Patients with and without Liver Disease Receiving Chloramphenicol and Oxytetracycline**

W. W. FALOON. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **44**, 75–90, July, 1954. 6 figs., 25 refs.

At the Hospital of the Good Shepherd, Syracuse, (State University of New York), nitrogen balance, riboflavin excretion, fat absorption, and liver histology and function were studied in patients with and without liver disease who were receiving either chloramphenicol or oxytetracycline. No alteration in nitrogen balance was observed in 4 patients during administration of chloramphenicol, but in 4 out of 5 patients receiving oxytetracycline urinary nitrogen excretion was significantly increased. Riboflavin excretion was related to nitrogen balance; there was no change in 3 patients when chloramphenicol was given, but in 2 patients significant changes occurred during the nitrogen catabolism observed when oxytetracycline was administered. The effect of administration of either agent upon nitrogen metabolism was not related to the presence or absence of liver disease. Liver function and the histological appearances of the liver were not changed by either antibacterial agent. In some cases there was a moderate increase in the number of stools during and immediately after administration of both chloramphenicol and oxytetracycline, but fat absorption was not affected.

A. W. H. Foxell

332. **Studies on the *in vitro* Activity of Anisomycin**

J. E. LYNCH, A. R. ENGLISH, H. BAUCK, and H. DELIGIANIS. *Antibiotics and Chemotherapy* [*Antibiot. and Chemother.*] **4**, 844–848, Aug., 1954. 5 refs.

A study of the activity *in vitro* of a new antibiotic, anisomycin, revealed that it was primarily effective against the protozoa. Its minimum inhibitory concentration against one strain of *Trichomonas vaginalis* and two strains of *Trichomonas foetus* was 1·56 to 3·12 μg. per ml. Four strains of *Entamoeba histolytica* were inhibited by 1·56 μg. per ml. and four strains of *Candida albicans* by 1·56 to 12·5 μg. per ml. of the drug. It has little antibacterial and antifungal activity.

Anisomycin was more active against *T. vaginalis* and *T. foetus* than 18 other drugs, and more active than 17 of the 18 against *E. histolytica*. Fumagillin was the only drug which was more active *in vitro* than anisomycin against *E. histolytica*.

A. W. H. Foxell

333. **Suppression of Certain Viral Lesions by a Microbial Product, Xerosin, Lacking in Demonstrable Antiviral Properties and Produced by *Achromobacter xerosis*, n.sp.** V. GROUPÉ, L. H. PUGH, A. S. LEVINE, and E. C. HERRMANN. *Journal of Bacteriology* [*J. Bact.*] **68**, 10–18, July, 1954. 5 figs., 17 refs.

Xerosin is prepared from actively growing cultures of *Achromobacter xerosis*, an aerobic, non-capsulated, non-spore-forming, Gram-negative rod obtained from the soil. In this report from Rutgers University, New Jersey, the suppressive action of this microbial product against the Nigg strain of mouse pneumonitis virus and its slight transient effect against influenza B virus are described. When xerosin was given by daily subcutaneous injection to mice 3 days after they had been infected with the Nigg virus the progress of the disease was arrested transiently, but this was not accompanied by a decrease in the infective titre of lung tissue.

Xerosin failed to affect viral synthesis *in vivo* and did not possess antiviral properties *in vitro*. It did not influence the cytopathogenic effect of Type-I poliomyelitis virus on epithelial cells in tissue culture. Some additive effect in suppressing mouse pneumonitis was observed when xerosin was administered with oxytetracycline, chlortetracycline, or chloramphenicol.

D. Geraint James

CHEMOTHERAPY OF TUBERCULOSIS

334. **Amithiozone as an Adjuvant to Isoniazid Therapy** V. C. BARRY, M. L. CONALTY, and E. E. GAFFNEY. *Irish Journal of Medical Science* [*Irish J. med. Sci.*] **6**, 299–303, July, 1954. 6 refs.

Amithiozone (thiacetazone) was shown by Domagk to inhibit the growth of human strains of *Mycobacterium tuberculosis* in concentrations of 0·1 to 1·0 μg. per ml. on solid egg medium. But though considerable attention has been paid to the use of streptomycin and PAS in combination with isoniazid in the treatment of tuberculosis, there has been less interest in combinations of thiacetazone and isoniazid.

The studies here reported from the laboratories of the Medical Research Council of Ireland, Dublin, were carried out *in vitro* and *in vivo*. Serial dilutions of thiacetazone were made in 5-ml. quantities of Proskauer–Beck medium containing 5% of human serum and inoculated with *Myco. tuberculosis* H37Rv or Ravenel Rv. Isoniazid-resistant strains were tested as well; these were maintained on Löwenstein medium containing 100 μg. of isoniazid per ml. Tests were made *in vivo* in both mice and guinea-pigs. The mice were infected with the Ravenel Rv strain or the isoniazid-resistant variant, and isoniazid and thiacetazone were administered in the diet for 14 days, beginning on the day of infection. The guinea-pigs were infected with the isoniazid-resistant variant of Ravenel Rv intradermally on the right flank and the left side of the thorax; an intradermal inoculation was also made on the right side of the thorax, using an isoniazid-sensitive strain of Ravenel Rv. In addition, a mixed inoculum of the resistant strain and the sensitive strain was injected subcutaneously into the left flank of each guinea-pig. Treatment with the drugs in the diet was usually begun after about 30 days, at which point a few control animals were killed and examined to note the degree of infection.

Thiacetazone was found to be much more active *in vitro* against isoniazid-resistant strains than against isoniazid-sensitive strains of *Myco. tuberculosis*, a concentration of 100 μg. per ml. being required for complete inhibition of growth of the sensitive strain after 28 days, compared with only 13·3 μg. per ml. for the isoniazid-resistant variant. Thiacetazone also delayed the emergence of resistant strains *in vitro*. This greater sensitivity of isoniazid-resistant strains to thiacetazone was confirmed *in vivo* in mice infected with tuberculosis. In animals infected with the isoniazid-resistant strain a prolongation of 30 days in the median survival time was obtained with doses of thiacetazone of 32 mg. per kg. body weight daily, a similar dose giving a prolongation of only 20 days in mice infected with the isoniazid-sensitive strain. The virulence of these organisms for mice was the same in both cases. It is suggested therefore that thiacetazone is a suitable adjuvant to isoniazid therapy.

R. Wien

335. **Experimental and Clinical Studies of a New Product Resulting from the Combination of Isoniazid with *p*-Aminosalicylic Acid.** (Étude expérimentale et clinique d'un produit nouveau résultant de la combinaison de l'isoniazide avec l'acide paramino-salicylique
R. KOURILSKY, S. KOURILSKY, and S. MICOULAUD. *Thérapie* [*Thérapie*] **9**, 273–292, 1954. 10 figs., 1 ref.

At the Centre de Pneumophtisiologie (Hôpital Saint-Antoine), Paris, the authors have studied a new anti-tuberculous drug produced by the molecular combination of PAS and isoniazid. This product, designated PIEM, is stated to be a chemical combination rather than a mixture of the two substances, is insoluble in water, possesses a molecular weight of 290, and has the empirical formula $C_{13}H_{14}O_4N_4$.

When administered orally to guinea-pigs experimentally infected with tuberculosis in daily doses of 25 to 50 mg. per kg. body weight for a period of 6 weeks, PIEM gave almost complete protection. No toxic effects were noted after daily doses of 40 mg. per kg. for 2 months, and in these doses, which are about 8 times greater than the usual dose of isoniazid, it was better tolerated. *In vitro* it was more active than isoniazid against a sensitive strain of tubercle bacillus, and it was effective against a strain of *Mycobacterium tuberculosis* H37Rv which was resistant to isoniazid.

The new product was tried in the treatment of 30 patients with pulmonary tuberculosis, and clinical details (including reproductions of radiographs) are given of 10 of these. Improvement was achieved in most of the cases, and in only one of the 30 was there some evidence of resistance to the drug after 2 months' treatment. It is active by mouth, well tolerated in a dose of 10 mg. per kg. body weight, and its therapeutic effect appears to be as good as that of streptomycin, PAS, or isoniazid. Its mode of action appears to resemble that of isoniazid.

R. Wien

Infectious Diseases

336. **The Prophylaxis and Treatment of Bacterial Complications of Measles with Benzethacil and Aqueous Procaine Penicillin G**
S. KARELITZ, C. C. CHANG, and Z. E. MATTHEWS. *Journal of Pediatrics* [*J. Pediat.*] **44**, 357–363, April, 1954. 9 refs.

One of the infections which was not prevented or which failed to respond to " benzethacil " was due to *Staphylococcus aureus*. Since an increasing number of strains of *Staph. aureus* is found to be penicillin resistant, the failure to control this infection is not surprising, and suggests the need for more extensive penicillin treatment or other antibiotics in some cases of measles. Likewise, the pneumonia which developed in a benzethacil-treated patient suggests an etiological agent which was not susceptible to the penicillin concentration created by the benzethacil.

The fact that a single injection of benzethacil was effective in 59 out of 61 cases and that penicillin injections given on alternate days were effective in all 47 cases is, however, quite significant. It is most important in the management of measles in hospitals since the need for nursing care as well as that of a physician is thereby sharply reduced. This is particularly welcome at a time when the shortage of nurses and house doctors is so acute. Furthermore it enables one to treat measles from the outpatient departments of hospitals provided adequate follow-up by doctors or visiting nurses is available to detect possible complications.

The fear of measles even if not modified by gamma globulin is sharply reduced by the knowledge that most complications can be avoided. While the morbidity is greater in measles treated by antibiotics than in measles modified by passive immunity through prophylaxis, it is conceivable that the former may result in greater or longer lasting immunity.

Encephalitis was not observed in the 255 patients studied, as was the case in the 135 patients previously observed. This is probably not significant, since measles encephalitis may be as uncommon as one in one to 4,000 cases. It is not likely that measles encephalitis will be prevented by penicillin or other antibiotic therapy if the current interpretations of the etiology of measles encephalitis are correct. The practical answer to this question will become known only after very large numbers of antibiotic-treated patients are compared to untreated patients.—[Authors' summary.]

337. **Respiratory Failure in the Acute Case of Poliomyelitis**
A. B. CHRISTIE. *British Medical Journal* [*Brit. med. J.*] **2**, 663–665, Sept. 18, 1954. 4 refs.

338. **Acute Disseminated Histoplasmosis with a Report of a Case Occurring in England**
F. C. POLES and J. D. O'D. LAVERTINE. *Thorax* (*Thorax*) **9**, 233–241, Sept., 1954. 11 figs., bibliography.

HELMINTHIC DISEASES

339. **Experiments in the Therapy of Human Ascariasis**
M. T. HOEKENGA. *American Journal of Tropical Medicine and Hygiene* [*Amer. J. trop. Med. Hyg.*] **3**, 755–761, July, 1954. 5 refs.

The author reports the results obtained with six different ascaricidal drugs used at a hospital in La Lima, Honduras, and in neighbouring labour camps in the treatment of 626 persons infected with *Ascaris lumbricoides*. Examination of the faeces for ova of *Ascaris* was made 10 days after completion of treatment and repeated 2 to 4 weeks later; no egg counts were carried out.

Diethylcarbamazine (" hetrazan ") was given in several different dosages, but the most effective was 12 mg. per lb. (26 mg. per kg.) body weight per day for 4 days. Of 30 cases treated at this dose level, 24 (80%) were free of *Ascaris* ova at both follow-up examinations. No side-effects were observed. Doses of 6 mg. per lb. (13 mg. per kg.) proved less satisfactory, and doses of 18 mg. per lb. (40 mg. per kg.) appeared to be too toxic to the 5 children who received it.

Sodium santoninate. The author points out that the structure of this compound renders it less toxic than santonin itself, and this was borne out in practice since, with doses several times larger than those recommended for santonin, no toxic effects were observed. The drug was given in flavoured cascara syrup. With single doses of 500 mg. the cure rate in 151 cases was 37·7%, while with multiple doses of 250 mg. for 6 days it was 53·3%.

" *Nematolyt*." This is a new German preparation containing the keratinolytic ferment papain; it is prepared from the paw-paw (*Carica papaya*). For it to be fully effective patients must be prepared by elimination of protein from the diet on the day preceding and on the day of treatment in order that the drug may exert its full action on the keratinous cuticle of the worms. A purge is given before and on the day after the single treatment. Of 8 patients so treated, 4 were cured.

Hexylresorcinol monoacetate. This substance may be given in liquid or tablet form without injury to the buccal mucosa. With the dose of 1 g. as recommended for hexylresorcinol itself the cure rate was poor, but of 6 patients given 3 g. daily for 4 days, cures were obtained in 4. No toxic side-effects were observed.

Hexylresorcinol enjoys a high reputation as an anthelmintic. The standard single dose of 1 g. was given to 80 patients, and resulted in a cure rate of 42%, a somewhat disappointing figure considerably lower than those reported elsewhere.

Oil of chenopodium. This drug was given as a mixture of one drop each of the oils of chenopodium, chloroform, eucalyptus, and menthol made up to 1 ml. with castor oil. The dosage was 1 ml. per year of age up to 12 years, and 15 ml. for adults, and the preparation was given on

an empty stomach. Of 80 patients treated, 32 (40%) were cured.

Discussing these results the author claims that though none is outstanding, some are encouraging. Better results have been reported by other workers, but their criteria of cure may have been less strict; in particular, the author stresses the importance of delaying examination of the stools until the 10th and 14th days after treatment, when female worms not expelled may have resumed egg-laying. He concludes that of the substances for single-dose treatment, hexylresorcinol gave the best result (42% cures), and of those for use in multiple dosage, diethylcarbamazine in a daily dose of 12 mg. per lb. (26 mg. per kg.) body weight for 4 days was the most promising (cure rate 80%). The author considers, however, that an ascaricidal agent more effective than any of these six compounds is required for mass treatment in Honduras. *O. D. Standen*

340. **The Oxygen Treatment of Ascariasis**
F. F. TALYZIN. *Lancet* [*Lancet*] **2**, 314–315, Aug. 14, 1954. 2 figs.

The author briefly describes the treatment of ascariasis introduced by Kravetz, which consists in the introduction under slight positive pressure of 1 to 2 litres of oxygen into the stomach of the fasting patient by means of a duodenal tube; if belching, nausea, or pain occurs, introduction of the gas is interrupted for 1 or 2 minutes. The gas soon leaves the stomach and produces uniform distension and tympanites; 2 hours later a saline aperient is given and after another 3 hours a normal meal is allowed. Dead worms are passed usually on the 2nd and 3rd days.

The necessary apparatus is simple and consists of two bottles connected by a rubber tube near their base; one of these contains water, while the other is filled with oxygen through an outlet at the neck fitted with a stopcock. The duodenal tube is connected to this outlet, and water is allowed to flow in from the first bottle, displacing the oxygen and delivering it at an easily controlled pressure.

No pain is produced by this treatment and no complications have been encountered. All the oxygen is absorbed within 2 to 3 hours. The pulse usually slows, but the blood pressure remains unchanged and the method is suitable for out-patient treatment. A further advantage is that no larvae develop from the ova present in the intestine. *Ferdinand Hillman*

341. **Ascariasis Treated with Piperazine Hydrate**
R. H. R. WHITE. *Lancet* [*Lancet*] **2**, 315–316, Aug. 14, 1954. 7 refs.

After a brief review of the literature concerning the use of piperazine in ascariasis the author reports 3 cases in children aged 2½ to 4 years which were treated with this drug. Starvation and purging were not employed in these cases, although it is stated that a mild saline purgative may be advisable if a heavy infestation is suspected. The dosages used in the 3 cases were, respectively, 68 mg. per kg. body weight per day for 10 days, 130 mg. per kg. for 7 days, and 81 mg. per kg. for an unspecified period. In all cases inanimate parasites were passed early in the course of treatment, subsequent barium *x*-ray studies failed to reveal any remaining worms, and the faeces remained free from ova. The course of treatment did not eliminate an associated infestation with *Trichocephalus trichiurus* in one case.

It is pointed out that irritation of the roundworm by anthelmintics may stimulate it to excessive activity and cause it to enter the common bile duct or penetrate the bowel wall. It has been shown by experiments *in vitro*, however, that piperazine produces progressive torpor of the worms without preliminary excitation, so that they become inert and are finally ejected with the faeces, though not necessarily dead. In the author's cases the worms, although motionless and apparently dead when discharged, were intact and of normal colour, which is seldom the case after treatment with tetrachlorethylene or oil of chenopodium. As all the children passed the worms in the early part of the course of treatment it may prove satisfactory to confine treatment to three days or even less. *Ferdinand Hillman*

342. **Treatment of *Ascaris lumbricoides* Infections with Piperazine Citrate**
H. W. BROWN and M. M. STERMAN. *American Journal of Tropical Medicine and Hygiene* [*Amer. J. trop. Med. Hyg.*] **3**, 750–754, July, 1954. 9 refs.

In a joint study carried out at the School of Public Health, Columbia University, and New York City Department of Health, 23 school-children were treated for ascariasis with an orange-flavoured, syrupy preparation of piperazine citrate (" antepar "), 1 ml. of which contained the equivalent of 100 mg. of piperazine hexahydrate. The usual dose was 0·5 or 1·0 g. of the drug twice daily for 3 (one case only), 4, 5, or 7 days. Egg-counts by the Stoll dilution method were made on the stools of each patient before, and again 2 to 3 weeks after, treatment in those cases showing ova of *Ascaris* in the faeces.

The results were highly satisfactory, 19 of the 23 patients being cleared of worms after a single course of treatment. Of 11 patients who received 7-day courses at home, 3 continued to pass eggs, but it is probable that these patients had not taken the full course of therapy. The patient treated for only 3 days also continued to pass eggs, but in all 4 of these cases of comparative failure the egg-counts were much reduced. Complete clearance was obtained in all cases in which the full course of treatment was given for 4 or 5 days under adequate supervision. Some patients reported the passage of worms on the 2nd or 3rd day of treatment, and in view of this finding it is suggested that a shorter course of treatment may be adequate in some cases. It is estimated that the minimum total dose of piperazine citrate required to produce a complete cure is about 0·15 g. per kg. body weight. No toxic side-effects were observed or reported, although total dosages of up to 0·466 g. per kg. were employed. It is concluded that piperazine citrate, which is readily taken by children and requires no preliminary fasting period, possesses great activity against *Ascaris lumbricoides* in man. *O. D. Standen*

BACTERIAL DISEASES

343. **Treatment of Early Whooping-cough with Chloramphenicol Palmitate**
D. MORRIS and W. C. COCKBURN. *Lancet* [*Lancet*] **2**, 724–726, Oct. 9, 1954. 1 fig., 3 refs.

Under the auspices of the Medical Research Council a controlled investigation was carried out to determine the results to be obtained in whooping-cough in young children by giving chloramphenicol palmitate as soon as the earliest symptoms are noted. All the children were family contacts of known cases of whooping-cough, and treatment was begun on the average about 6 days from the onset of symptoms and was continued for 7 days. Alternate patients were given a suspension which was similar in appearance to that of the palmitate but did not contain chloramphenicol. The dosage [which seems adequate] was 1 g. daily for children under 11 months, 1·5 g. daily for children aged 12 to 35 months, and 2 g. daily for those aged 36 to 59 months. Each child was observed for a period of 28 days from the start of treatment, during which time the parent recorded the number of paroxysms each day and whether the paroxysms were mild, moderate, or severe. This assessment of the number and the severity of the paroxysms was checked once a week when the patient attended the clinic and at least once a week by a nurse who visited the patient's home.

Briefly, it was found that paroxysms were considerably fewer and less severe in the treated children than in the control group, especially from about the 9th to the 20th day after the start of treatment. Before and after this period the differences were small, but after the 25th day none of the paroxysms in either group was considered to be severe. Bacteriologically, it was much more difficult to isolate *Haemophilus pertussis* from swabs taken between the 3rd and 7th days from the treated group than it was from similar swabs from the control group, but after that time the proportion of positive cultures in the treated group was only slightly less than that in the control group.

It is concluded, therefore, that with this treatment whooping-cough is not cured or aborted, but is modified for a time. Bronchopneumonia occurred during treatment in 2 of the controls and in one patient given chloramphenicol; no conclusion is therefore drawn concerning the influence of chloramphenicol in preventing complications. The authors point out that general practitioners are unlikely to be able to treat cases at an earlier stage than was the case in this investigation, so the value of chloramphenicol palmitate in whooping-cough must be regarded as strictly limited. Since it may sometimes cause untoward sequelae it is not wise for practitioners to use this drug as a routine.

[Although it is notoriously difficult to assess results in whooping-cough, great care was obviously taken in this investigation to obtain reliable data; and although there were only 23 treated cases and 27 controls, the findings can, in these circumstances, be considered of value. A larger experience might show that the modification of the disease in the second and third weeks is of value in reducing such complications as bronchopneumonia and collapse which often develop about this time.]

H. Stanley Banks

344. **The Treatment of Whooping-cough with Antibiotics. Comparative Bacteriological, Clinical, and Experimental Investigations.** (Beitrag zur Behandlung des Keuchhustens mit antibiotischen Mitteln. Vergleichende bakteriologische, klinische und tierexperimentelle Untersuchungen)
E. WERNER. *Monatsschrift für Kinderheilkunde* [*Mschr. Kinderheilk.*] **102**, 341–344, July, 1954. 1 fig., 17 refs.

The author reports that whereas streptomycin, chloramphenicol, aureomycin, and oxytetracycline ("terramycin") were found to be equally effective in inhibiting the growth of *Haemophilus pertussis in vitro*, clinical trial of the first three in cases of whooping-cough gave different results. Of 99 children treated at the Children's Clinic of the Free University of Berlin during the past 3 years, 56 received streptomycin, 21 chloramphenicol, and 22 aureomycin. Each drug was given for approximately 6 days, streptomycin in doses of 50 mg. per kg. body weight (later increased to 100 mg.), chloramphenicol in doses of 100 mg. per kg., and aureomycin in doses of 25 to 50 mg. per kg. daily. From an analysis of the results of treatment the author concludes that streptomycin is inferior to the other two antibiotics, the best results being obtained with aureomycin. In an attempt to explain the discrepancy between the results obtained *in vitro* and the clinical effectiveness of the drugs, experiments were carried out on rabbits in which suspensions of *H. pertussis* in saline, alone and with streptomycin, chloramphenicol, aureomycin, oxytetracycline, or penicillin, were injected intracutaneously. All caused the same degree of necrosis after 24 to 48 hours, and it is concluded that this was due to small amounts of free endotoxin present in the suspensions rather than to bacterial action. Injection of a control suspension which had been boiled for 10 minutes, thereby destroying the endotoxin, caused no change in the skin. In another series of experiments mice were infected by the intranasal instillation of two drops of a culture of *H. pertussis* containing 800 to 1,000 million organisms per ml. Most of the untreated control mice died, their lungs post mortem showing a picture of interstitial pneumonia resembling in many respects that seen in the lung in human pertussis, but mice treated with streptomycin by injection or with aureomycin, chloramphenicol, or oxytetracycline by mouth for 10 days after infection survived in about 90% of cases, there being no difference in effectiveness between the four antibiotics. The author suggests that the clinical manifestations of infection with *H. pertussis* are due to its toxic effects on the tissues and that antibiotics can be effective only if given sufficiently early to eliminate the infection before toxin has been produced in harmful amounts.

Franz Heimann

345. **Treatment of Tetanus with Succinylcholine**
A. T. T. FORRESTER. *British Medical Journal* [*Brit. med. J.*] **2**, 342–344, Aug. 7, 1954. 7 refs.

Tuberculosis

DIAGNOSIS AND PROPHYLAXIS

346. **Revaluation of the Flourpaper Tuberculin Jelly Test**

M. CAPLIN, J. HARRINGTON, C. P. SILVER, and S. GRZYBOWSKI. *British Medical Journal* [*Brit. med. J.*] **2**, 895–898, Oct. 16, 1954. 12 refs.

The investigation here reported was undertaken in order to compare the accuracy of the tuberculin jelly test with that of the Mantoux test. Both plain and flourpaper jelly tests were carried out, the latter entailing light abrasion of the skin with Gauge-00 sandpaper, and the results were read in accordance both with the standard of positivity accepted by the Medical Research Council (erythema and oedema, with or without vesiculation) and with those laid down by Dick (4 or more vesicles or papules after 72 hours) and by Lendrum (6 or more vesicles or papules after 96 hours). All three tests were carried out together on 288 children of 5 to 15 years, 115 of whom gave a positive reaction to the Mantoux test with 1 : 100 old tuberculin. When the result of the flourpaper jelly test was read after 72 hours according to the first standard the result was negative in 39 (34%) of these 115 children. By using the other standard the number of false negative reactions was reduced to 18 (16%), but positive results were obtained in 18 (10%) of the 173 Mantoux-negative children. At 96 hours there were no false positive reactions, but a higher proportion of Mantoux-positive children gave negative reactions.

In a further investigation the results of simultaneous flourpaper jelly tests and Mantoux tests on 108 children were read independently after 72 and 96 hours by 4 non-expert observers. While there was unanimous agreement in 96% of cases on the result of the Mantoux test at 96 hours, only in 68% did a majority of the 4 observers agree on the result of the patch test. Finally, simultaneous Mantoux tests and flourpaper jelly tests were carried out on 437 children and the results of each test were read independently by 2 observers with experience of the method concerned. Agreement between the observers was obtained in 99·8% of cases with the Mantoux text, but in only 63·4% of cases with the jelly test. The authors conclude that the flourpaper tuberculin jelly test is unsatisfactory for use either in clinical practice or in tuberculin surveys. *Franz Heimann*

347. **Recognition of Tuberculosis in Children under 2 Years**

F. J. W. MILLER and R. MCDOUGALL. *British Medical Journal* [*Brit. med. J.*] **2**, 846–848, Oct. 9, 1954. 6 refs.

It is pointed out that present-day treatment of the early stages of tuberculous meningitis and miliary tuberculosis is now so effective that recognition of the primary lesion is essential. In the child of 2 years the capacity to localize infection is not fully developed, and the risk of miliary tuberculosis and tuberculous meningitis is therefore greater than it is in older children.

Records were studied of 313 children seen in hospitals and tuberculosis clinics in Newcastle upon Tyne between 1946 and 1950 who were known to have been infected in the first 2 years of life, the object being to demonstrate ways in which tuberculosis becomes manifest. Of these 313 children, 150 were first seen when admitted to hospital ill, the remainder being seen initially as contacts. In 253 children there was radiological evidence of lung infection and in 28 the presenting sign was enlargement of cervical lymph nodes. In 256 (82%) there was known contact with an infective adult.

Symptoms in about one-third of the 150 children admitted to hospital were due to the primary lung complex, and included failure to gain weight, a harsh, dry cough, and a wheeze becoming louder on coughing. In a further one-third tuberculous meningitis was present, the early symptoms being listlessness, irritability, interruption or alteration of consciousness, and neck stiffness; the authors emphasize the importance and at the same time the difficulty of detecting neck stiffness. Lymphadenitis was found in 28 of these 150 children and bone or joint tuberculosis in 10.

Diagnosis is usually made by a combination of tuberculin tests and radiological examination. The authors consider that the tuberculin test is of first importance in young children; in their view a positive result does not mean that any particular illness is tuberculous in origin, but it emphasizes the possibility, or indeed with a young child the probability, that it is so. They prefer the intradermal (Mantoux) test, especially if diagnosis is urgent, and suggest that tuberculin tests should be carried out as a routine in infant welfare centres and general practice. *Elaine M. Osborne*

RESPIRATORY TUBERCULOSIS

348. **Cerebral Manifestations in the Course of Pulmonary Tuberculosis.** (Manifestations encéphaliques au cours de la tuberculose pulmonaire)

H. WAREMBOURG and G. NIQUET. *Presse médicale* [*Presse méd.*] **62**, 1175–1176, Aug. 28, 1954. 6 refs.

From the Neurological Clinic of the University of Lille the authors describe 4 interesting cases of encephalitic manifestations occurring in adults in the course of pulmonary tuberculosis. In none of them were clinical signs of meningitis present, and the cerebrospinal fluid (C.S.F.) was normal in all. The clinical picture varied from case to case, but onset was usually sudden. Three patients had symptoms of a confusional state, and 3 were febrile. All had gross evidence of neurological lesions in the form of hemiplegia or multiple involvement of cranial nerves, or a combination of these. Gross

papilloedema was present in 2 cases, but radiographs of the skull were normal in all. The electroencephalogram showed diffuse cerebral dysrhythmia without evidence of a focal lesion in all cases. One patient died 6 months after the onset of the encephalitic illness, but necropsy was not performed. The other 3 recovered, the neurological and psychological signs and symptoms disappearing, but 2 of these suffered up to 3 relapses of the same syndrome separated by years of remission, one dying eventually of Addison's disease [but necropsy does not appear to have been performed].

The authors speculate on the nature of the disease and suggest that it may be analogous to the leuco-encephalitis which occurs in the course of certain acute infectious fevers, and that it may have an allergic basis. (In support of this they quote a fifth case, that of a child of 8 who was admitted soon after B.C.G. vaccination with headache, vomiting, confusion, and hemiparesis. The C.S.F. was normal and he made a rapid recovery within 15 days. Allergy to B.C.G. was regarded as a possible aetiological factor.) Alternatively, the attack may have been due to vascular causes, hypotension being a prominent finding in one of the cases. *John Lorber*

349. **The Pulmonary Tuberculoma in Childhood: Its Medical and Surgical Management**
K. E. KASSOWITZ. *Journal of Pediatrics* [*J. Pediat.*] **45**, 153–163, Aug., 1954. 11 figs., 9 refs.

The author selected 11 typical cases of various forms of pulmonary tuberculosis in childhood from a total of about 1,000 cases admitted to the Muirdale Sanatorium and Milwaukee Children's Hospital, and on the basis of these discusses the course of the disease and the indications for surgical treatment. He considers that surgery is only exceptionally indicated, because the prominent part played by the hilar lymph nodes does not permit limited resection of the pulmonary component. The response of secondary lesions in children to chemotherapy or to collapse therapy is usually satisfactory, even if giant cavities are present. The only death in this small group, and one of the very few fatalities in the whole series, was due to shock following attempted pulmonary resection. *John Lorber*

350. **Indefinitely Prolonged Chemotherapy for Tuberculosis. Preliminary Report**
A. S. DOONEIEF and K. E. HITE. *American Review of Tuberculosis* [*Amer. Rev. Tuberc.*] **70**, 219–227, Aug., 1954. 8 refs.

The results are reported of prolonged administration of two or more chemotherapeutic agents in 49 cases of pulmonary tuberculosis at the Montefiore Hospital, New York. The ages of the patients, who were unselected, ranged from 14 to 64 years, and all were being treated for tuberculosis for the first time. The pulmonary lesions were minimal in 6 cases, moderately advanced in 37, and advanced in 6. Varying combinations of streptomycin, PAS, and isoniazid were given for 13 to 22 months. Streptomycin was usually given daily for 1 to 3 months, and thereafter 2 to 3 times weekly; the dosage of isoniazid was 4 mg. per kg. body weight daily and that of PAS was 12 to 15 g. daily. In the patients with minimal lesions the sputum, which was positive at the start of treatment, became negative within one month. The clinical response and the improvement in the chest radiographs were " excellent " in all 6 cases, and there were no relapses. The sputum was positive in 36 of the 37 cases of moderately advanced pulmonary disease, and in 28 of these it became negative in 1 to 12 months. In none of the patients in this group was there clinical or radiological evidence of relapse, but in 7 the sputum was positive 8 to 20 months after the start of treatment. A good therapeutic response was obtained in all 6 patients with far advanced disease, the sputum becoming negative within 4 months; in 2 cases, however, the sputum was positive 10 and 14 months respectively after treatment started. In this group also there was no clinical or radiological evidence of relapse.

Drug toxicity was slight and all patients were able to continue treatment. Patients receiving streptomycin complained of headache, malaise, drowsiness, and circumoral paraesthesiae on the days they received the drug.

The authors suggest that in view of the frequency of relapse in patients given chemotherapy for short periods, the results obtained in the present series indicate that " the time has come to explore very prolonged, perhaps life-long, treatment with antimicrobial agents in some patients ". The possible limiting factors are drug toxicity, the attitude of the patient to continued treatment, and bacterial resistance; the authors state that this last " has not presented a problem to date ". Although bacteriological relapse—that is, reappearance of tubercle bacilli in the sputum—was observed in 6 cases in this series during treatment, the authors consider that the preliminary results are far better than those achieved with " any previously available therapy for tuberculosis ". *John Taubman*

351. **The Results of Treatment of Pulmonary Tuberculosis with Streptomycin, PAS, and Isoniazid Given Together for Three Months.** (Résultats du traitement de la tuberculose pulmonaire par streptomycine, P.A.S. et isoniazide appliqués en association pendant trois mois)
É. BERNARD, B. KREIS, A. LOTTE, P. LOUBRY, and J. COBY. *Revue de la tuberculose* [*Rev. Tuberc.* (*Paris*)] **18**, 149–166, 1954. 4 figs.

In this paper from the Hôpital Laënnec, Paris, the authors compare the results of treating 157 cases of pulmonary tuberculosis with streptomycin, isoniazid, and PAS given in combination with the results achieved with isoniazid alone in 199 comparable cases in the series previously reported by Lotte and Poussier (*Rev. Tuberc.* (*Paris*), 1953, **17**, 1; *Abstracts of World Medicine*, 1953, **14**, 197). The authors' 157 cases included 121 of recent onset (6 months or less) and 36 older cases; 27 patients in each of these subgroups had previously received chemotherapy. The doses employed were 5 mg. of isoniazid per kg. body weight daily, 1 g. of streptomycin every third day, and 15 g. of PAS daily.

The clinical response to treatment in the authors' groups and in the earlier group was very much the same

in regard to reduction of fever and quantity of sputum, increase in weight, and signs of radiological improvement, with a slight bias in favour of the group receiving the combined treatment. Bacteriologically, the proportion who became sputum-negative after 3 months was identical in the two groups. The really striking difference between the groups was in the rate of development of bacterial resistance. Of the authors' patients, after 3 months' treatment 85% remained completely sensitive to isoniazid, 91% to streptomycin, and 83% to PAS, although whereas 83% were sensitive to all three drugs before treatment, this figure fell to 63% after 3 months. The proportion resistant to isoniazid was therefore only 15% at 3 months; in the earlier series this figure was 80% at the same period. The authors stress the value of combined therapy, in that it permits of more prolonged treatment before the development of bacterial resistance. *T. M. Pollock*

352. **Acute Perifocal Reaction in Tuberculosis due to PAS**

S. L. O. JACKSON. *Tubercle* [*Tubercle (Lond.)*] **35**, 188–194, Aug., 1954. 10 figs., 6 refs.

In this paper from the Luton Chest Clinic 3 cases of pulmonary tuberculosis are described in which administration of PAS produced an acute reaction around tuberculous tissue. Two of the patients who were receiving PAS and streptomycin became febrile and chest radiographs revealed an increase in the extent and density of opacities. The general and pulmonary reactions were attributed to PAS. The third patient, who had tuberculous cervical adenitis, reacted similarly during treatment with PAS alone; in this case the cervical lymph nodes became enlarged and tender. A year later when PAS was once more tried the same reactions were observed. Subsequently this patient was given streptomycin and isoniazid, which were well tolerated.

J. R. Bignall

353. **Isoniazid and P.A.S. in Chronic Pulmonary Tuberculosis. A Warning**

C. L. JOINER, K. S. MACLEAN, J. D. CARROLL, K. MARSH, P. COLLARD, and R. KNOX. *Lancet* [*Lancet*] **2**, 663–666, Oct. 2, 1954. 3 figs., 11 refs.

The authors have studied the results of two different treatment schedules in a series of 27 patients with chronic fibrocaseous tuberculosis who were treated and observed for 6 months at Guy's Hospital, London. The patients were divided into two comparable groups, thus: Group IP, in which 14 patients were treated with 250 mg. of isoniazid and 10 g. of PAS daily. Group R (rotating) contained 13 patients, who were treated for 4 weeks with 250 mg. of isoniazid daily and 1 g. of streptomycin intramuscularly twice weekly, then for 4 weeks with streptomycin and PAS (10 g. daily by mouth), and then for 4 weeks with PAS and isoniazid; during the subsequent 12 weeks the above cycle was repeated.

Up to 12 weeks scarcely any difference was noted between the two groups. However, after 12 weeks it became obvious that the number of sputum-positive cases in Group IP, which had at first fallen, was increasing, whereas there was a continuous fall in the number in Group R. Also, more cases of drug resistance appeared in Group IP than in Group R. Although the radiological and weight changes were inconclusive, the erythrocyte sedimentation rate fell more rapidly in patients in Group R. These findings are discussed and compared with those for other, similar series reported in the literature, the authors pointing out that if the trial had been ended at 12 weeks they would have had to conclude that isoniazid and PAS were at least as effective as rotating therapy. Since it is becoming increasingly clear that courses of chemotherapy for chronic tuberculosis must be very long, they issue the warning that in their opinion, for the reasons given, the combination of isoniazid and PAS alone is not suitable for this purpose and that treatment schedules, such as the rotating one described, which will reduce the incidence of drug-resistance are much to be preferred.

Paul B. Woolley

354. **Recent Trends in Survival of Patients with Respiratory Tuberculosis**

C. R. LOWE. *British Journal of Preventive and Social Medicine* [*Brit. J. prev. soc. Med.*] **8**, 91–98, July, 1954. 10 figs., 8 refs.

Since the beginning of the present century mortality from most infectious diseases has been falling steadily. In some cases the rate of fall has increased dramatically since the end of the last war, respiratory tuberculosis being one such disease. In Birmingham the death rate from this cause was halved between 1910 and 1945, a period of 35 years, but it was halved again between 1945 and 1951, a period of only 6 years, the most striking fall in mortality occurring between 1949 and 1952, when the rate fell from 54 to 25 deaths per 100,000 of the population. Since there has been no sudden decline in the incidence of the disease, this improvement can probably be attributed to improved prognosis as a result of the introduction of effective chemotherapy, and in the present paper the author analyses the subsequent history of patients notified in Birmingham during the past 20 years to determine whether there has in fact been a marked change in the survival rate.

Between 1913 and 1938 the notification rate for respiratory tuberculosis in Birmingham decreased from 483 to 96 per 100,000 of the population—a fall of 80%. During the same period mortality fell from 119 to 70 per 100,000—a fall of only 41%. The author suggests that even though the notification rate is an unreliable index of incidence, this difference is sufficiently striking to permit the improvement in mortality to be attributed largely to a decline in morbidity. The very great fall in mortality since 1939, however, has not been accompanied by a fall in the notification rate; in some years, indeed, the latter has increased, although this may be the result of more intensive case-finding and may not represent the true trend of morbidity.

The records of all patients notified as suffering from respiratory tuberculosis in each of the 8 years 1930, 1935, 1940, 1945, 1947, 1949, 1950, and 1951 were examined at the Birmingham Chest Clinic and the date each one was last seen alive (or, where applicable, the date and

cause of death) was determined. In addition, each case was classified in one of 3 groups according to the state of the disease on notification, Group I consisting of relatively mild cases and Group III of the most severe. Life tables were then prepared for the patients notified in each of the above years showing the estimated number alive on each anniversary of notification per 1,000 patients, and graphs constructed from these. Of those patients who were notified in 1930 and 1935, only about 60% survived one year, about 30% 5 years, and about 20% 10 years. In contrast, about 70% of those notified in 1947 survived one year and 50% 5 years. This improvement in the survival rate occurred among cases of all three types. Since 1947 the improvement in prognosis appears to have been maintained. It is concluded that the remarkable post-war fall in mortality, " although possibly associated with some decline in incidence, is largely attributable to improvement in prognosis at every stage of disease ".

The author makes a limited examination of the effect of sex and age at notification on the survival rate with particular reference to patients notified in 1935, on whom a 10-year follow-up was possible. Male patients appeared to survive longer than females in Group I, but in Group III females fared better than males. Irrespective of the state of the disease, young males (under 35) had a better chance of survival than young females, but older males had a slightly worse chance than older females. Sex differences were also found in the age distribution of morbidity. For females this was at a maximum in young adult life (age 20 to 24) ; the male notification rates, however, had two peaks, one at age 20 to 24 and the other at age 50 to 54 following a secondary rise after age 40. But whereas the age distribution of morbidity of females was much the same whatever the state of the disease, amongst males Group-I disease was almost entirely limited to young adults and Group-III disease to the elderly, while the age distribution in Group II reflected the bimodal distribution in all groups combined. *E. A. Cheeseman*

EXTRA-RESPIRATORY TUBERCULOSIS

355. **Comparison of the Effect of Streptomycin plus *p*-Aminosalicylic Acid and Streptomycin plus Isoniazid on Tuberculous Lesions of the Kidneys**
J. C. DICK. *Lancet* [*Lancet*] **2**, 516–522, Sept. 11, 1954. 16 figs., 7 refs.

At Robroyston Hospital, Glasgow, the histological appearances in the kidneys of 25 patients with renal tuberculosis who had been treated with streptomycin and PAS were compared with those observed in the kidneys of 25 similar patients treated with streptomycin and isoniazid and in tuberculous kidneys from 46 patients who had not received chemotherapy. It was found that streptomycin with PAS checked the development of the lesions and induced fibrosis and some regression, whereas streptomycin with isoniazid resulted in complete resolution of acute lesions and resolution modified by secondary pyogenic infection in chronic lesions. These differences were attributed to "a more fundamental antituberculous action of isoniazid by which epithelioid cells revert to macrophages, fibrosis does not develop, and the body is able to repair a lesion more completely with greater absorption of necrotic tissue, increased vascularity, and more epithelial regeneration ". *J. B. Enticknap*

356. **Spinal Cord Complications of Tuberculous Meningitis. A Clinical and Pathological Study**
W. D. W. BROOKS, A. P. FLETCHER, and R. R. WILSON. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **23**, 275–290, July, 1954. 11 figs., 15 refs.

The authors have studied the incidence of complications involving the spinal cord in a consecutive series of 80 patients treated for tuberculous meningitis at St. Mary's Hospital, London, between 1947 and 1953. Most of their patients were adults and all 10 who developed " transverse myelitis " (defined by the authors as " a complete or partial transverse lesion of the spinal cord occurring in the presence of tuberculous meningitis ") were 18 years of age or older. The series was weighted with complicated cases, patients unsuccessfully treated elsewhere in the region being referred to the hospital for investigation. The onset of the " transverse myelitis " was sudden in 8 cases and gradual in 2. It was present at the onset of the disease in one case, but in the others it usually appeared several months later. Of the 15 cases in the whole series in which spinal block occurred, myelitis developed in 7, indicating a significant correlation between the two conditions. A level of sensory loss was determined in 7 cases, all in the thoracic region. The chief disability was paraplegia in extension or flexion. Four of the 10 patients died, but in the 6 survivors recovery, although gradual and taking several months, was almost complete neurologically.

Details are given of the post-mortem findings in cases of " transverse myelitis ", which are contrasted with those in patients who died with evidence of spinal block only. In the latter group, although both dura and arachnoid showed extensive tuberculous changes, the cord itself was normal. Vascular lesions similar to those found in the cerebral vessels were present in both groups, but were considerably more numerous in the former group. In two of the most long-standing cases the dura and the arachnoid were fused with fibrous tissue and there was much softening in the cord.

The authors do not consider that treatment with PAS or isoniazid has led to a reduction in the incidence of spinal complications [which is in contrast to the experience of others] and feel that an agent which would prevent the development of the fibrinous exudate or remove it when formed is more likely to be effective in this respect. *John Lorber*

357. **Specific Immunization in the Treatment of Children with Tuberculous Meningitis.** (Spezifische Immunisierung bei der Behandlung von Kindern mit tuberkulöser Meningitis)
H. GENZ. *Monatsschrift für Kinderheilkunde* [*Mschr. Kinderheilk.*] **102**, 448–450, Oct., 1954. 22 refs.

Venereal Diseases

SYPHILIS

358. The Victoria Blue (Berger Kahn) Flocculation Test for the Serological Diagnosis of Syphilis

H. GREENBURGH and B. J. STEPHENS. *Guy's Hospital Reports* [*Guy's Hosp. Rep.*] **103**, 174–181, 1954. 6 refs.

The Victoria blue (V.B.; Berger–Kahn) flocculation test for the diagnosis of syphilis, first described by Berger (*J. Path. Bact.*, 1943, **55**, 363), is a slide test of relatively simple technique in which the dye Victoria blue 4R is used as a sensitizing agent and as an indicator of the occurrence of flocculation when serum from a syphilitic patient is added to a mixture of compound tincture of benzoin and Kahn antigen.

The authors applied this test in parallel with the Wassermann and Kahn reactions to all sera sent to the clinical pathological laboratory of Guy's Hospital, London, for routine testing for syphilis during the first 5 months of 1950, during which time 2,116 samples of serum were tested. Complete agreement between the 3 tests was obtained in 1,845 cases (87·2%). In 162 instances the V.B. test gave a doubtful (±) result with sera from patients with no clinical evidence of syphilis and with which the Wassermann and Kahn tests were negative. It was decided, therefore, to classify doubtful V.B.-test results as negative and to accept only a positive result (+) or greater degree (++) as indicating a positive reaction to the test. This gave complete agreement between the 3 tests in a further 7·65% of cases, giving a total of 94·85% with full agreement. [Doubtful Wassermann reactions were, however, classed as positive.]

In no instance was it found that an untreated case of confirmed syphilis gave a negative result with the V.B. test. Negative V.B.-test results were found in association with positive Wassermann and/or Kahn reactions in 34 instances. In only 12 of these cases did further investigations lead to a diagnosis of syphilis, and all 12 patients had received antisyphilitic treatment. In another group of 26 sera giving positive V.B.-test results in the presence of negative Wassermann and Kahn reactions it was found that 5 samples of serum were from cases of early untreated syphilis, 3 from cases of late untreated syphilis, 15 from cases of treated syphilis, and one from a case of general paralysis; in the remaining 2 cases no information was available.

The authors conclude that the V.B. test, on account of the stability of the antigen, the small amount of serum required, and the ease and rapidity with which the test can be carried out, is very suitable for use in laboratories where large numbers of sera have to be screened for evidence of syphilis. They recommend that sera giving a positive reaction should be further examined by other tests in order to confirm the result and eliminate false positive reactions. *A. J. King*

359. Effect of Calcium Ion on the Kolmer Complement-fixation Test

A. S. BROWNE, M., M. MICHELBACHER, and E. M. COFFEY. *American Journal of Clinical Pathology* [*Amer. J. clin. Path.*] **24**, 934–945, Aug., 1954. 3 figs., 18 refs.

While carrying out the Kolmer complement-fixation test in the laboratories of the California State Department of Health the authors experienced difficulties due to low complement titres and to fluctuations in titre which could not be explained by variation in the reagents used, but showed a rough correlation with the purity of the distilled water. With the addition of calcium to the saline used, however, consistently high and constant titres were obtained, 0·04 g. of $CaCl_2.2H_2O$ per litre of saline being found to be the optimum level. Parallel complement titrations carried out with and without added calcium and with varying periods of primary incubation showed that when primary incubation was omitted altogether the addition of calcium made no difference to the titre, but it increased the titre slightly when incubation periods of ½ hour at 37° C. and of 16 hours at 4° to 6° C. plus 10 minutes at 37° C. were used. With an initial dilution of complement in the two salines of 1 : 50 instead of the usual 1 : 30 in the presence of 0·2 ml. of inactivated normal serum and with a primary incubation period of 16 hours at 4° to 6° C. plus 10 minutes at 37° C. there was less non-specific destruction of complement when calcium was added. This was also the case in control tests in which no serum was added. With 12 sera the 100% titre (the dilution of complement in 1 ml. that just gives complete haemolysis) ranged from 62 to 125 in saline without calcium and from 71 to 125 in saline with calcium. In subsequent work the 100% titre was taken as the actual titre found rather than the arbitrary upper limit of 1 : 43 set by Kolmer.

Parallel tests with the two salines on 532 specimens of serum or cerebrospinal fluid (C.S.F.) showed that of 252 (231 sera and 21 C.S.F.) which were reactive to the V.D.R.L. slide test, 42 were reactive to the Kolmer test only with added calcium; 16 sera gave anticomplementary reactions—7 with both salines, 7 with added calcium only, and 2 with Kolmer saline only. A comparison of the results of the V.D.R.L. slide test with those of the standard Kolmer test on 160,984 sera showed that 4·3% were negative to the latter but reacted to the former. In similar tests carried out on 47,701 sera in which calcium was added to the saline and complement used at the titrated dilution this figure was 3·5%.

The authors conclude that the addition of 40 mg. of $CaCl_2.2H_2O$ per litre of Kolmer saline is of value in giving high complement titres, increasing sensitivity, and stabilizing the test results. If is this done the magnesium added should be the chloride instead of the usual sulphate to avoid precipitation of insoluble calcium sulphate. *A. E. Wilkinson*

360. Use of Calcium Saline Solution in Kolmer Complement-fixation Test

J. A. KOLMER and E. R. LYNCH. *American Journal of Clinical Pathology* [*Amer. J. clin. Path.*] **24**, 946–953, Aug., 1954. 6 refs.

The effects of adding calcium to the saline used in the Kolmer complement-fixation test as recommended by Browne *et al.* [see Abstract 359] have been examined by the authors at Temple University School of Medicine, Philadelphia. Enhancement of the complement titre was found to occur in 78 out of 80 complement titrations, the titres for two full Kolmer complement units in 50 of the tests being equal to or less than the absolute minimum of 1·0 ml. of a 1 : 43 dilution laid down by Kolmer. A slight increase in haemolysin titres was also noted.

Parallel quantitative Kolmer tests were carried out using saline with and without the addition of 0·04 g. of $CaCl_2.2H_2O$ per litre on 85 syphilitic and 61 non-syphilitic sera and on 12 specimens of syphilitic and 28 of non-syphilitic cerebrospinal fluid (C.S.F.). Stronger reactions were given by 27 syphilitic sera with the added calcium and by 6 without, while 55 of the non-syphilitic sera gave negative reactions to both tests, but 6 showed incomplete lysis of the controls, with possible false positive reactions, in the test with added calcium. In the tests on C.S.F., 8 of the syphilitic group gave a stronger reaction with added calcium and one without, while 23 of the non-syphilitic fluids gave negative reactions in both tests, but 5 showed incomplete lysis of the controls, with some possible false positive reactions, in the test with added calcium.

The authors conclude that while the addition of calcium to the saline enhances complement activity and the sensitivity of the Kolmer test, it may be wise to set an arbitrary limit of not less than 0·35 ml. of 1 : 30 dilution of complement as the exact unit, or 1·0 ml. of 1 : 37 dilution as 2 full Kolmer units, when the test is performed under these conditions. If higher dilutions are used incomplete lysis of controls and possible false positive reactions may occur, particularly with C.S.F.

A. E. Wilkinson

361. The Decline and Fall of Syphilis in New York State, 1936–1953. II. Early Congenital Syphilis

R. L. VOUGHT, L. DE MELLO, and W. R. AMES. *American Journal of Syphilis, Gonorrhea and Venereal Diseases* [*Amer. J. Syph.*] **38**, 361–370, Sept., 1954. 1 fig., 3 refs.

The annual attack rate for early congenital syphilis (that is, syphilis in infants under 1 year of age) in New York State has been reduced by approximately 98% since the inauguration of a syphilis control programme in 1936 and, since 1950, has become steady at about 7 cases per 100,000 live births. The effectiveness of the control measures is indicated by this steady decline in the incidence of early congenital syphilis in spite of an increase in the annual attack rate for early acquired syphilis between 1943 and 1951. These measures include the obligatory reporting of cases of syphilis to the public health authorities, provision of a free serological diagnostic service to physicians, obligatory treatment of all infectious cases and infected contacts, obligatory prenatal and premarital serological tests, free supply of penicillin for the treatment of syphilis, and education of the population and physicians. During the same period the prevalence of syphilis among parents decreased by 58%, although it remains high (1·3%).

It is inferred that syphilis transmission in the State has now reached a steady level, but since this level is relatively high there is no assurance that severe outbreaks will not occur in the future, particularly if population movement is increased or control measures are lessened.

V. E. Lloyd

362. Time–Dosage Relationship in the Treatment of Treponemal Diseases with a New Combination of Three Penicillin Salts. Laboratory and Clinical Basis for Effective Therapy

C. R. REIN, F. H. BUCKWALTER, C. H. MANN, S. E. LANDY, and S. FLAX. *American Journal of Syphilis, Gonorrhea and Venereal Diseases* [*Amer. J. Syph.*] **38**, 408–412, Sept., 1954. 12 refs.

A combination of three salts of penicillin is advocated by the authors for the treatment of treponemal diseases. Each dose of 2 ml. contains in aqueous suspension 300,000 units of potassium benzylpenicillin, 300,000 units of procaine benzylpenicillin, and 600,000 units of N:N′-dibenzylethylenediamine di(benzylpenicillin). Higher and more prolonged blood levels were obtained with a single injection of 2 ml. than with a single injection of 4 ml. of procaine penicillin in oil with 2% aluminium monostearate (P.A.M.), although both contain 1,200,000 units of pencillin. Initial trials in syphilis, yaws, and pinta are reported as giving highly encouraging results [but no clinical details are given]. It is suggested that this type of penicillin preparation is suitable for use in those countries where patients must be treated with a single injection.

V. E. Lloyd

363. The Occurrence of Malignant Disease in Syphilitic Individuals

P. D. ROSAHN. *American Journal of Syphilis, Gonorrhea and Venereal Diseases* [*Amer. J. Syph.*] **38**, 413–421, Sept., 1954. 8 refs.

The incidence of malignant disease at necropsy in 276 persons with syphilis, as diagnosed from historical, clinical, laboratory, or post-mortem evidence, is compared with that in two control groups of 355 and 353 non-syphilitic subjects drawn at random from the same series of 3,907 necropsies on persons of 20 years or more performed in the Department of Pathology of Yale University between 1917 and 1941. It was found that malignant disease in general, without regard to type or primary site, occurred no more frequently in syphilitic than in non-syphilitic individuals. There was some evidence, however, that in syphilitic persons with malignant disease the primary lesion is located in the tongue more frequently than in non-syphilitic persons with malignant disease, and also that carcinoma of the cervix is more common among syphilitic than among non-syphilitic women with cancer, but in neither case was the number of cases sufficient to permit any valid conclusion to be drawn.

V. E. Lloyd

GONORRHOEA

364. **The Effects of the Administration of Erythromycin upon *Neisseria gonorrhoeae* and Pleuropneumonia-like Organisms in the Uterine Cervix**
A. RUBIN, N. L. SOMERSON, P. F. SMITH, and H. E. MORTON. *American Journal of Syphilis, Gonorrhea and Venereal Diseases* [*Amer. J. Syph.*] **38**, 472–477, Sept. 1954. 15 refs.

In the 5-year period 1935–40 before penicillin was available the average number of reported cases of gonorrhoea in the United States was some 175,000 per year; in the last 5 years the figure has been about 200,000 per year. In view of this continuing incidence of gonorrhoea and the ill health due to its sequelae (notably chronic pelvic inflammatory disease) the authors, working at the University of Pennsylvania, Philadelphia, decided to test the efficacy of the newer antibiotic erythromycin, which is reputed to be effective against organisms resistant to other antibiotics. In discussion they also point out that it may be significant that other investigators have isolated pleuropneumonia-like organisms (P.P.L.O.) from the uterine cervix of approximately 80% of women suffering from gonorrhoea.

Erythromycin to a total dose of 3·6 g. was administered orally to 24 female out-patients with gonococcal infection, confirmed by isolation of the organism, three 100-mg. tablets being taken 4 times a day for 3 days. In 22 cases (92%) cultures for the gonococcus were negative, and remained so in 18 cases for 3 successive weeks; of the 2 unsuccessful cases, in one the organism was still present after treatment and in the other it reappeared after an interval of 2 weeks. None of the patients developed signs or symptoms suggestive of gonorrhoea of the upper genital tract. Erythromycin had no discernible effect on P.P.L.O. Before treatment 18 patients (75%) had both gonococci and P.P.L.O. present in the cervix, and after treatment P.P.L.O. could still be isolated in 16 of them (67%). Side-reactions occurred in 19 (79·2%) of the patients, in the form of diarrhoea, abdominal cramps, nausea, and vomiting, and 16 patients developed temporary vulvar or anal itching, but in no instance were the symptoms severe enough to require discontinuation of therapy. *Neville Mascall*

365. **Oral Tetracycline Hydrochloride for the Treatment of Acute Gonorrhea in Males**
W. I. METZGER, M. MARMELL, and A. PRIGOT. *American Journal of Syphilis, Gonorrhea and Venereal Diseases* [*Amer. J. Syph.*] **38**, 480–482, Sept., 1954. 2 refs.

The newly developed antibiotic tetracycline is readily absorbed and widely diffused throughout the body; in particular it is excreted in high levels in the urine, a finding which the authors consider is of great importance in treating infections of the genito-urinary tract such as gonorrhoea.

At Harlem Hospital, New York, 50 male patients suffering from acute gonorrhoea were treated with a total dosage of 1·0 g. of tetracycline. Cure resulted in 44 cases, a cure-rate of 88%. This was not quite as good as that obtained with chlortetracycline (aureomycin) in a comparable series, in which the cure rate was 94·3%. In another group of 24 patients suffering from the same complaint and treated with a total dosage of 1·5 g. of tetracycline there were no failures, a cure rate of 100%. No drug toxicity was observed in any of the patients. *Neville Mascall*

366. **N:N′-Dibenzylethylenediamine Dipenicillin G Given Orally for the Treatment of Gonorrhea**
R. R. WILLCOX. *American Journal of Syphilis, Gonorrhea and Venereal Diseases* [*Amer. J. Syph.*] **38**, 469–471 Sept., 1954.

The results of treatment of 74 patients suffering from gonorrhoea with N:N′-dibenzylethylenediamine di-(benzylpenicillin) given orally in a flavoured syrup base are reported. In 46 cases single oral doses ranging from 600,000 units to 4·8 mega units were given, the remaining 28 patients receiving two doses, each of 2·4 mega units, at an interval of 6 hours.

Of the former group, 44 were followed up for periods up to 201 days. Of these, 16 were definite failures, 7 were considered to be cases of reinfection, 3 more had non-specific infections, and only 18 (40%) could be regarded as cured. Of 23 out of the 28 given two doses and followed up for a maximum period of 177 days, 14 (60%) "had no subsequent incident" and 4 were definite failures.

It is concluded that this product given in single orally-administered doses of up to 4·8 mega units is of little value in the treatment of gonorrhoea. The results of giving two doses of 2·4 mega units at an interval of 6 hours were somewhat better. *Neville Mascall*

367. **Oral Penicillin with and without Benemid in the Treatment of Gonorrhea**
A. JACOBY, J. POLLOCK, and V. BOGHOSIAN. *American Journal of Syphilis, Gonorrhea and Venereal Diseases* [*Amer. J. Syph.*] **38**, 478–479, Sept., 1954. 3 refs.

368. **The Question of the Penicillin Sensitivity of Gonococci.** (Zur Frage der Penicillinempfindlichkeit der Gonokokken)
K. MARCUSE and H. HUSSELS. *Dermatologische Wochenschrift* [*Derm. Wschr.*] **130**, 1031–1044, 1954. 1 fig., 22 refs.

At the County Medical Research Laboratories, Berlin, the sensitivity to penicillin of gonococci obtained from cervical and urethral smears in 232 cases of gonorrhoea was investigated between 1950 and 1952. By dividing cultures into a number of subcultures various degrees of resistant gonococci were grown; the authors' methods are described in detail. The limit of penicillin sensitivity was reached at a concentration of 0·06 unit of penicillin per ml. of medium, at which level no growth was obtainable. When such cultures were allowed to continue growing the gonococci always reverted to a more sensitive strain; this biological characteristic is thought to explain the fact that no penicillin-fast gonococci have so far been found. The authors believe that there is little likelihood of such a change occurring. *G. W. Csonka*

Tropical Medicine

369. **Xerophthalmia in the Presence of Kwashiorkor**
H. A. P. C. Oomen. *British Journal of Nutrition* [*Brit. J. Nutr.*] **8**, 307–318, 1954. 1 fig., 19 refs.

The clinical condition of 29 Indonesian children aged between 7 months and 7 years who were suffering from severe malnutrition, xerophthalmia, and keratomalacia is reported in detail from the Stella Maris Hospital, Macassar, Indonesia. It was notable that no cases of xerophthalmia were seen in Chinese children, although one-third of the beds in the hospital were occupied by them. This discrepancy is attributed to the different feeding habits of the two races—Chinese children generally get enough milk and protein, but Indonesian children live chiefly on rice, and even in hospital it was difficult to persuade them to accept milk, meat, or fish. Although it was not possible to determine carotene or vitamin-A levels in the blood it appeared from the dietary history that while the diet contained satisfactory amounts of carotene it was poor in vitamin A.

Most of the children were admitted for illnesses other than the eye condition. Body weight was 30 to 50% below the expected level for age, many of them were so weak that they could hardly sit without support, and most were oedematous and anaemic. In 16 cases phrynoderma was present, but " crazy-pavement " skin, regarded as one of the principal signs of kwashiorkor in Africa, was observed in only 6 cases and depigmentation of the hair in 8. Most of the children suffered from respiratory infections, diarrhoea, and anorexia, and forced feeding had to be instituted as a matter of urgency in about half of the cases. Glossitis and atrophy of the oral mucosa was present in 14 cases, and intermittent steatorrhoea in a further 8. Liver biopsy showed fatty infiltration of the liver in 21 out of 22 cases so examined. Lack of lustre of the cornea was found in all cases; 26 of the patients had active xerophthalmia and 14 keratomalacia in one or both eyes, while there were 6 cases of corneal ulcer and 6 of perforation. Of the 25 survivors, 22 left hospital with tolerably good vision in at least one eye.

Routine treatment consisted in adding to the normal hospital diet 50 g. of green vegetables and 50 g. of mashed liver daily and the administration of 10 ml. of cod-liver oil three times daily. This regimen was usually successful in clearing up the ocular lesions within 7 days; the general malnutrition, however, was less amenable to treatment. Of the 29 patients, 4 died after the eye condition had improved and 2 more were removed from hospital in a hopeless state. While xerophthalmia seems to be rare in kwashiorkor in Africa, it is a frequent complication in Indonesia. In spite of the diarrhoea and abnormal state of the liver, cod-liver oil by mouth proved a quick and effective remedy; the comparatively ample carotene content of the diet on the other hand seemed to replace but poorly the lack of vitamin A. Malnutrition is a major public-health problem in Indonesia, and in the author's experience is more often due to ignorance and mistaken feeding habits than to poverty.

Z. A. Leitner

INFECTIOUS DISEASES

370. **Treatment of Scrub Typhus in the Pescadores Islands with Chloramphenicol, Aureomycin and Terramycin**
A. P. Prezyna, Chang Teh-Ling, Wang Tsu-Lin, W. J. Dougherty, and H. B. Bond. *American Journal of Tropical Medicine and Hygiene* [*Amer. J. trop. Med. Hyg.*] **3**, 608–614, July, 1954. 9 refs.

The authors report the results of treatment with antibiotics of 47 cases of scrub typhus occurring among Chinese Nationalist troops in the Pescadores Islands in the South China Sea. The disease appears to be identical with the Malayan scrub typhus, an eschar being identified in all but 2 cases. These 2 cases showed serum titres of 1 : 160 and 1 : 1,280 respectively against *Proteus* OX-K, and in addition had typical symptoms of the disease. Rickettsiaemia was demonstrated by mouse inoculation in 9 of 10 samples of blood examined.

In treatment, chloramphenicol was given in 25 cases, aureomycin in 12 cases, and " terramycin " (oxytetracycline) in 10 cases. At first a single dose of 6 g. was given with all 3, but this caused vomiting and treatment was altered to 2 doses of 3 g. each, and finally to an initial dose of 3 g. followed by a dose of 2 g. 12 hours later. All three drugs were about equally effective, the average duration of fever after therapy being shortest in patients receiving chloramphenicol, namely, 40 hours compared with 48 and 49 hours respectively in those given aureomycin and oxytetracycline. The relapse rates were also much the same for all three drugs and ranged between 17 and 20%. It is noteworthy that in this, as in previously reported series, relapses were more frequent in cases treated early in the disease; relapses are said to be very rare in patients treated after the 7th day of fever. The authors consider that the development of natural immunity contributes to a more rapid defervescence and cure in conjunction with antibiotic therapy. The Pescadores strains of *Rickettsia orientalis* are closely similar to Malayan strains in their response to these antibiotics.

William Hughes

371. **Hemorrhagic Fever. I. Epidemiology**
I. H. Marshall. *American Journal of Tropical Medicine and Hygiene* [*Amer. J. trop Med. Hyg.*] **3**, 587–600, July, 1954. 2 figs., 19 refs.

The author gives a comprehensive account, including a brief survey of the now fairly extensive literature, of the epidemiology and the clinical and pathological features of haemorrhagic fever as observed among

United Nations troops in the Korean war. The clinical features are now well recognized: onset is abrupt, following one or two days of prodromal malaise; initially the temperature may reach 105° F. (40·6° C.), but usually returns to normal within a week; vomiting and headache are prominent early symptoms. The haemorrhages appear from the 6th to the 8th days, scleral haemorrhage being characteristic; there is also albuminuria with an associated oliguria, and post mortem the cortex of the kidney is found to be dark red and the medulla pale, while the pituitary gland shows extensive focal necrosis. The characteristic haemorrhages may be found in any organ of the body.

Reviewing the literature, the author notes that the Japanese had recognized a haemorrhagic fever in Manchuria in 1939 which appeared to be clinically and epidemiologically similar to, if not identical with, the haemorrhagic fever occurring in Korea. They regarded it as a virus disease transmitted by the mite *Laelaps jettmari*, a parasite of the field mouse *Apodemus agrarius*. The Russians have suggested that the vector is a flea, the reservoir of infection being in the vole *Microtus michnoi*. So far, United States investigators have not been able to confirm or refute either of these claims. The seasonal distribution of the fever shows a peak in May–June and another in October–November. Field surveys have shown that *A. agrarius* is commoner than any other species of rodent in Korea. The mite *L. jettmari* was recovered from rodents in the endemic area but was not shown to be host specific. Trapping operations gave a fairly uniform yield of these mites all the year round with no definite peaks; on the other hand the occurrence of larval forms of trombiculid mites showed biphasic peaks in late April and October, that is, 2 weeks before the peaks in the incidence of haemorrhagic fever—a finding which the author considers very suggestive, although no evidence has been found of patients being attacked by such a vector. The available data point strongly to a mite as vector and a rodent as the reservoir of infection, but exact identification of both must await further study. *William Hughes*

372. **Hemorrhagic Fever. II. Prevention**
S. C. DEWS and I. H. MARSHALL. *American Journal of Tropical Medicine and Hygiene* [*Amer. J. trop. Med. Hyg.*] 3, 601–607, July, 1954. 1 fig., 2 refs.

In view of the findings previously reported [see Abstract 371] which suggested that haemorrhagic fever is due to an insect-borne virus from a rodent reservoir, and adding their observations to other epidemiological findings, the authors, working with the U.S. Eighth Army Group in Korea, considered there was sufficient evidence to justify a campaign against mites in the area occupied by troops in the field. The technique and results of this campaign are here described.

The attack on the mites was threefold: (1) individual protection by treating clothing with mite repellents; (2) control of rodents by trapping and poison baiting; and (3) spraying of tents and bunkers with 1% lindane (gammabenzene hexachloride). The predominant rodent was the field mouse *Apodemus agrarius* and " warfarin " as a poison bait was extremely effective. The authors give a detailed account of the difficulties encountered in impregnating clothing with a mite repellent. The repellents used were dibutylphthalate, dimethylphthalate, and benzyl benzoate, either singly or as a combination of all three. The most effective method was to impregnate the clothing while it was being laundered. It was not easy to provide comparable figures showing results of treatment, since the conditions under which the troops lived were not uniform before and after the campaign had started. The authors did observe, however, clear-cut results in one company of soldiers who did physical training in non-impregnated shorts and shirts during July, 1952; 14 cases of haemorrhagic fever occurred in this unit in 27 days. Thereafter the men wore impregnated clothing for their training and no further cases occurred. It is considered that the use of mite repellents and rodent control provide a high degree of protection against the disease. *William Hughes*

373. **Fumagillin in the Treatment of Amebiasis**
R. L. BLACK, L. L. TERRY, and C. G. SPICKNALL. *Gastroenterology* [*Gastroenterology*] **27**, 87–92, July, 1954. 8 refs.

At the U.S. Public Health Service Hospital, Baltimore, 30 cases of amoebiasis received fumagillin in doses of 10 mg. 3 times daily for 14 days, the total dose being 420 mg. [apparently given by mouth]. In 17 of the cases there were no symptoms and these patients were regarded as carriers, their faeces containing only cysts. Of the other patients, 11 either had active diarrhoea or a recent history of it, while the other 2 showed symptoms of liver involvement. These last 2 patients improved under treatment with fumagillin, but one of them subsequently required the administration of emetine. Of the 17 carriers, 9 were re-examined 6 weeks later, when the stools were found to be free from *Entamoeba histolytica* in all 9. In all of the 11 cases with diarrhoea the stools were negative at the end of treatment, but 4 weeks later, when 7 of them were re-examined, amoebae were found in the stools in 2 cases. No definite toxic effects were observed in any of the patients. *F. Hawking*

374. **Amebic Granuloma. Report of Four Cases and Review of the Literature**
C. G. SPICKNALL and E. C. PEIRCE. *New England Journal of Medicine* [*New Engl. J. Med.*] **250**, 1055–1062, June 24, 1954. 4 figs., bibliography.

Four cases of thickening and tenderness of the colon due to amoebiasis in which the clinical picture closely resembled that of acute appendicitis or carcinoma are described. In the first case laparotomy was performed for what was thought to be an appendix abscess, and in 2 others a hard annular stricture of the rectum closely simulated primary carcinoma. Granulomatous thickening of the colon or rectum due to necrosis with secondary bacterial infection was considered to be the cause of the lesion in every case.

From their experience and a study of the literature the authors believe that granuloma of the colon is a less

common complication of amoebiasis than either hepatitis or hepatic abscess. Two-thirds of the lesions occur in the caecum and rectum, a distribution similar to that seen in uncomplicated amoebiasis. Occasionally more than one granuloma may occur at the same time or in succession. The usual presenting symptoms are bloody diarrhoea, pain, and local tenderness with a palpable mass; fever is not common. Radiological examination is of value only in determining the site of the lesion, not its nature. Amoebae are usually, but not invariably, present in the stools, while the complement-fixation test for amoebiasis is negative in most cases. Response to conservative treatment may be the only sure guide to the correct diagnosis. In the authors' view surgical treatment should be restricted to emergency care of complications, infection of the skin, haemorrhage, and peritonitis being likely sequelae of surgical measures. No single anti-amoebic drug is recommended in the treatment of this condition; in the majority of cases the lesion disappears within a month. *D. W. Barritt*

375. **Functional and Needle Biopsy Study of the Liver in Malaria**

L. G. WHITE and A. A. DOERNER. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **155**, 637–639, June 12, 1954. 14 refs.

Liver function was investigated at the U.S. Public Health Service Hospital, Staten Island, New York, in 37 cases of malaria, 19 of which were due to *Plasmodium falciparum*, 14 to *P. vivax*, and 2 to *P. malariae*, while in 2 the infecting agent was unidentified. Biopsy was carried out with the Vim–Silverman needle in 7 cases (3 *P. falciparum* and 4 *P. vivax*), and the liver function tests performed included the following: cephalin–cholesterol flocculation, thymol turbidity, gamma globulin turbidity, zinc sulphate turbidity, and "bromsulphalein" excretion tests, determination of serum bilirubin level, prothrombin time, serum total protein content and albumin : globulin ratio, and serum content of cholesterol and cholesterol esters.

Abnormal reactions were observed in most cases and were "similar to those one might expect to see in acute infective hepatitis". The results of most tests returned to normal after antimalarial treatment. Except for pigment granules in the Kupffer cells and the presence of eosinophils [presumably within the vessels], no abnormalities were seen in the biopsy material, which was obtained "2 to 7 days after treatment".

The authors conclude that the abnormal results of liver function tests in malaria are probably due to diffuse involvement of the reticuloendothelial system. There was no evidence of chronic hepatitis arising as a sequel to malaria.

[The results of the liver function tests are similar to those reported by many other authors. The significance of the biopsy examinations is doubtful and depends on factors not presented in the paper—for example, the severity of the infection, its duration before treatment, the method of treatment, and the exact stage at which the biopsy material was taken, time being a very important factor in the development or recession of hepatic damage.] *B. G. Maegraith*

376. **The Pattern of Hepatic Dysfunction in Malaria**

G. W. LOOMIS, P. HELLER, W. H. HALL, and H. J. ZIMMERMAN. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **227**, 408–416, April, 1954. 6 figs., 44 refs.

A number of different liver function tests were carried out at two U.S. Veterans Administration Hospitals on 75 men recently returned from Korea who were infected with *Plasmodium vivax* and were being treated either with chloroquine or with quinine and pentaquine. The patients had taken chloroquine regularly as suppressive treatment, and only 3 had had attacks of malaria in Korea. The results of the tests were in agreement with those reported by other workers. Those most frequently found abnormal were the flocculation reactions, abnormalities of which continued into convalescence. Impairment of "bromsulphalein" excretion was also common, but appeared early in the course of the illness and was transitory.

The literature concerning impairment of liver function in malaria is briefly discussed. It is concluded that since the impairment of bromsulphalein excretion must be due to some transient mechanism it may be "a reflection of decreased delivery of the dye to the hepatic cell because of decreased blood flow and not necessarily a reflection of parenchymal damage". The authors point out that abnormality of the flocculation reactions is related to disturbance of the plasma proteins, which may occur from both hepatic and extrahepatic causes; they consider that the relation of the persistence of abnormal reactions to dysfunction of the liver is not well established, and that the reticuloendothelial system may be involved.

[In the authors' discussion of the literature the abstracter is misquoted as stating that the decreased hepatic blood flow "is the result of fever".] *B. G. Maegraith*

377. **Sickling and Malaria**

R. A. MOORE, W. BRASS, and H. FOY. *British Medical Journal* [*Brit. med. J.*] **2**, 630–631, Sept. 11, 1954. 3 refs.

The authors have studied the association between malaria and the sickle-cell trait in two tribes on the coast of Kenya with widely different sickle-cell-trait rates, results concerning 302 Daruma and 220 Kambe being presented. The incidence of parasitaemia in both groups was 61%, while that of sickling was 10% in the Daruma and 34% in the Kambe. The proportion with an enlarged spleen was not significantly different as between the two tribes. The survey was restricted to two small areas, and in order to test the homogeneity of the data the results were studied in small sets in the order in which they were collected. After allowance had been made for non-homogeneity of the data in the Daruma, no association between sickling and parasitaemia, nor between sickling and an enlarged spleen, was found in either tribe.

Thus the suggestion of Allison (*Brit. med. J.*, 1954, **1**, 290) that sickling affords protection against malaria has not been confirmed in the field. *J. L. Markson*

Allergy

378. **The Influence of the Thyroid Gland on the Histamine and Anaphylactic Reactions in Animals. I. The Influence of Thyroidectomy on the Sensitivity of Guinea-pigs to Aerosols of Histamine and Acetylcholine.** [In English] Å. NILZÉN. *Acta allergologica* [*Acta allerg.* (*Kbh.*)] 7, 231–245, 1954. 7 refs.

It has previously been shown experimentally in animals that the anaphylactic reaction is enhanced by administration of thyroid preparations, as also is tuberculin allergy and epidermal allergy.

In the present group of experiments, the first of a series carried out at the Karolinska Institute, Stockholm, the author sought to determine whether suppression of thyroid function altered the resistance of guinea-pigs to aerosols of histamine and acetylcholine. Thyroid activity was suppressed by thyroidectomy or reduced by injection of radioactive iodine. It was found that depression of thyroid activity caused increased resistance to histamine and acetylcholine, and that when thyroxine was administered the resistance to these substances was lowered. *A. W. Frankland*

379. **Prolonged Cortisone and Hydrocortisone Therapy** C. E. ARBESMAN and N. B. RICHARD. *Journal of Allergy* [*J. Allergy*] **25**, 306–311, July, 1954. 14 refs.

At the General and Children's Hospitals, Buffalo, New York, a total of 63 patients suffering from severe or moderately severe asthma were treated with cortisone (300 mg. on the first day, 200 mg. on the seond, 100 mg. on the third, and thereafter a maintenance dose of 50 to 75 mg. a day) or hydrocortisone (240 mg., 160 mg., and 80 mg. on the first three days, then 40 to 60 mg. daily), both drugs being given by mouth. The treatment was continued for long periods—in some cases for over 2 years. About two-thirds of the patients reported "good" or "excellent" results, while one-quarter obtained "fair" relief. There was no significant difference between the effects of cortisone and hydrocortisone in the dosage used. *H. Herxheimer*

380. **Comparative Results of the Use of ACTH, Cortisone, and Hydrocortisone in the Treatment of Intractable Bronchial Asthma and Pulmonary Emphysema** H. A. BICKERMAN and A. L. BARACH. *Journal of Allergy* [*J. Allergy*] **25**, 312–324, July, 1954. 2 figs., 27 refs.

At the Presbyterian and Goldwater Memorial Hospitals (Columbia University), New York, a total of 163 patients with bronchial asthma and emphysema of the bronchospastic type were treated with ACTH (corticotrophin), cortisone, or hydrocortisone, some of them with repeated courses. ACTH (100 mg. daily for 4 to 5 days, or 60 mg. in gel form daily for 5 to 6 days) was given to 67, cortisone (300 mg. daily for 2 days, then 200 mg. daily for 3 days and 100 mg. daily for 5 days, intramuscularly or orally) was given to 61, and hydrocortisone (160 to 200 mg. for 4 days, then 80 to 100 mg. for 6 days orally) was given to 35 patients. A complete or partial remission of symptoms resulted from 82% of 130 courses of ACTH, from 86% of 123 courses of cortisone, and from 96% of 56 courses of hydrocortisone. The relief became manifest within 18 to 36 hours with hydrocortisone, 24 to 48 hours with ACTH, and 4 to 5 days with cortisone. Adverse side-reactions were least frequent with hydrocortisone. The remission lasted 2 to 3 weeks, and in patients with pulmonary emphysema the remission was usually less complete than in those with uncomplicated bronchial asthma. It is concluded that 50 to 60 mg. of hydrocortisone is therapeutically equivalent to 100 mg. of cortisone in asthma. The effect of hydrocortisone was the same in subsequent courses as in the initial course, but this was not always so with cortisone and ACTH.

[More complete and longer lasting remissions would probably have been achieved in the patients with chronic bronchitic changes if the courses had been longer than 6 to 10 days.] *H. Herxheimer*

381. **Asthma and the Liver.** (Asthme et foie) J. TURIAF and P. BLANCHON. *Annales de médecine* [*Ann. Méd.*] **55**, 176–191, 1954. 30 refs.

In a study of the digestive upsets associated with asthma in 25 subjects by means of a battery of liver function tests, including puncture biopsy, the authors were unable to find any evidence of hepatic insufficiency. Their findings suggested to them that the digestive upsets were due to reactions in the biliary passages resembling those occurring in the bronchi, and resulting in spasm and atony of the gall-bladder and bile ducts, secretory disturbances, and inflammatory reactions. *J. Pepys*

382. **Atmospheric Mold Spores in and out of Doors** M. RICHARDS. *Journal of Allergy* [*J. Allergy*] **25**, 429–439, Sept., 1954. 3 figs., 32 refs.

The relative importance of the air indoors and the air outside as sources of mould spores which can cause respiratory allergy was studied at St. David's Hospital, Cardiff. In a normal dry house free from damp, Petri dishes containing Sabouraud's medium were exposed to room air daily for a period of 12 months, similar plates being exposed in the outside air. It was found that the moulds collected indoors were the same as those caught outside, and moreover they were caught in approximately similar proportions. There were strong seasonal fluctuations—for example, the number of colonies of *Cladosporium* and *Epicoccum* reached a peak during July and August. The moulds found in damp houses were also of the same species as those found outside, but the predominating type differed from house to house, the species prevailing in any particular house most probably being governed by local ecological factors.

H. Herxheimer

Nutrition and Metabolism

383. **The Renal Element in Rachitic Aminoaciduria**
J. H. P. Jonxis and T. H. J. Huisman. *Lancet* [*Lancet*] **2**, 513–516, Sept. 11, 1954. 6 refs.

In 3 rachitic children, 2 of whom had resistant rickets, and 3 healthy children the plasma and urine levels of amino-acids were estimated. Plasma levels in the rachitic children were normal, and the levels of histidine and of arginine, before and during intravenous administration of these amino-acids, were no higher than in the controls. Intravenous administration of histidine to the rachitic children caused a five- to ten-fold increase in excretion of this amino-acid as compared with the controls, but little or no change in the excretion of arginine. Excretion of serine, lysine, glycine, threonine, and, sometimes, tyrosine in children with rickets increased slightly following intravenous administration of histidine or arginine. Vitamin D is considered to facilitate the reabsorption of histidine and possibly other amino-acids. *F. W. Chattaway*

384. **Experimental Observations on the Tetany of Potassium Deficiency**
P. Fourman. *Lancet* [*Lancet*] **2**, 525–528, Sept. 11, 1954. 23 refs.

In an experimental study carried out at the University of Cambridge potassium deficiency was induced in 2 healthy human subjects by the administration of an ammoniated exchange resin and gave rise to mild tetany, which occurred several days after the period of administration of the resin. Nitrogen and electrolyte balance studies were performed. There was a considerable potassium deficit after ingestion of the resin, but only small changes occurred in the sodium level and an acidosis was present. The tetany was accompanied by a slight fall in the serum calcium level and a mild alkalosis developed. It was notable that sodium retained in the cells in place of potassium was not lost immediately on restoring the potassium level after depletion; it was at this point that the tetany occurred, accompanied by increased excitability of nerve fibres. The various possible mechanisms concerned in its production are discussed at some length and it is concluded that it may be concerned with intracellular ionic levels.
F. W. Chattaway

385. **Treatment of Gout with H.P.C.**
D. N. Ross. *British Medical Journal* [*Brit. med. J.*] **2**, 782–786, Oct. 2, 1954. 6 refs.

The author, from the General Hospital, Newcastle upon Tyne, describes the results obtained with 3-hydroxy-2-phenyl-4 cinchoninic acid (HPC), a derivative of cinchophen, in the treatment of 10 cases of gout, and briefly records 2 further cases. The dosage was 1 to 2 g. daily for an initial period, usually a few days, then 0·5 to 1 g. daily.

Satisfactory results were obtained in acute gout, apparently quite as good as some obtained with colchicine. The drug was also effective in the chronic type of gouty arthritis, but in these cases more prolonged treatment was necessary. Administration of the drug had often to be interrupted, however, because of troublesome skin reactions; erythema was a frequent early reaction and vesiculation was observed later in 6 cases. Nevertheless, the drug was persevered with, in some cases for long periods; one patient received a total of 210 g. of HPC within a trial period of 9 months. No serious toxic effects were observed; nausea and diarrhoea, which occurred in some cases, could usually be prevented by giving the drug in small doses after the main meals with an equal amount of sodium bicarbonate. In the author's view HPC should be reserved for short-duration treatment of acute gout or for prophylactic treatment of patients with premonitory symptoms.
Joseph Parness

386. **Ascorbic Acid Requirements and Urinary Excretion of *p*-Hydroxyphenylacetic Acid in Steatorrhoea and Macrocytic Anaemia**
R. J. Boscott and W. T. Cooke. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **23**, 307–322, July, 1954. 5 figs., 40 refs.

This paper describes the use of the technique developed by the senior author (*Biochem. J.*, 1952, **51**, xlv) for the estimation of hydroxyphenylic acids in urine by paper chromatography in a study of the urinary output of *p*-hydroxyphenylacetic acid (PHPA) in cases of macrocytic anaemia and its relation to depletion of ascorbic acid.

In 20 cases of macrocytic anaemia associated with steatorrhoea investigated at the Queen Elizabeth Hospital, Birmingham, large amounts of PHPA were shown to be excreted, as also was the case in 5 patients with megaloblastic anaemia of pregnancy. On the other hand 5 patients with pernicious anaemia excreted only small amounts of PHPA and this quickly disappeared when they were given ascorbic acid, while PHPA was found in significant amounts in the urine of only 4 of 25 normal subjects and again disappeared after the administration of ascorbic acid. The patients with steatorrhoea were very resistant to ascorbic acid in this respect, requiring larger doses administered over longer periods before PHPA excretion was reduced, even when the ascorbic acid was given parenterally. Three patients showed a haematological response to continued administration of ascorbic acid.

The view is advanced that " the refractory macrocytic anaemia, the abnormal ascorbic-acid utilization, and the disturbed tyrosine metabolism in these patients are manifestations of a common underlying metabolic error ". *D. A. K. Black*

Gastroenterology

387. **Post-hepatitis Cirrhosis**
P. C. REYNELL. *Lancet* [*Lancet*] **2**, 215–216, July 31, 1954. 11 refs.

Between 1940 and 1948, 14 unequivocal cases of post-hepatitis cirrhosis were seen at the Radcliffe Infirmary, Oxford. Of the 14 patients, 9 died and 5 recovered to the extent that over a follow-up period of at least 6 years none showed clinical evidence of impaired liver function, and the response to liver function tests became normal. Jaundice, which was persistent or recurred up to the time of recovery or death in some cases, was a striking clinical feature.

Ascites developed early in the disease in 6 cases, but cleared up completely in 5. The cause of death was hepatic failure and coma in 8 of the 9 fatal cases.

G. A. Smart

388. **Subdivision of Hexagonal Liver Lobules into a Structural and Functional Unit. Role in Hepatic Physiology and Pathology**
A. M. RAPPAPORT, Z. J. BOROWY, W. M. LOUGHEED, and W. N. LOTTO. *Anatomical Record* [*Anat. Rec.*] **119**, 11–33, May, 1954. 11 figs., 13 refs.

In order to study the anatomy of the liver in experimental animals the authors, working at the University of Toronto, injected red and black gelatin masses simultaneously into two main branches of the portal vein, sections of the liver being then prepared and examined microscopically. The same technique was used for injection of the hepatic artery and bile ducts. The authors reject the concept of the fundamental structural unit of the liver as a hexagonal lobule orientated around a central vein, and believe that the basic structural and functional units are berry-like masses of parenchyma around the triad of terminal branches of portal vein, hepatic artery, and bile duct. They explain, in terms of their theory, the distribution of ischaemic necrosis and other lesions seen in various pathological conditions.

P. C. Reynell

STOMACH AND DUODENUM

389. **Hypoglycemia in Relation to Duodenal Ulcer**
L. C. BECK. *Journal of the American Geriatrics Society* [*J. Amer. Geriat. Soc.*] **2**, 422–428, July, 1954. 7 refs.

For the purpose of studying the incidence of hypoglycaemia in duodenal ulcer, 96 patients seen at the Straub Clinic, Honolulu, with symptoms of gastro-intestinal disease were divided into 2 groups: (1) 47 patients in whom there was radiological evidence of duodenal ulcer; and (2) 49 patients with symptoms simulating those of duodenal ulcer but in whom no radiological evidence of ulceration could be found. In 9 of the patients in the second group no free hydrochloric acid was found in the gastric contents following histamine stimulation, and these 9 patients were therefore studied separately. Free hydrochloric acid was present in all the remaining patients in this group and in all those with duodenal ulcer.

The glucose tolerance test showed that 24 of the patients with proved duodenal ulcer had hypoglycaemia—that is, a blood sugar level at one time or another of 70 mg. per 100 ml. or less—whereas only 5 of the 40 patients in the non-ulcer group had hypoglycaemia. Except in one case, these hypoglycaemic levels were found at 2 and 4 hours after administration of glucose. None of the 9 achlorhydric patients without duodenal ulcer had hypoglycaemia.

The findings are taken to indicate that " moderate hypoglycaemia following a carbohydrate meal is one of the several factors responsible for increased gastric acidity ".

Joseph Parness

390. **Relationship of Ulcer Pain to *p*H and Motility of Stomach and Duodenum**
E. R. WOODWARD and H. SCHAPIRO. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol. (N.Y.)*] **86**, 504–506, July, 1954. 1 fig., 11 refs.

The exact cause of the pain in peptic ulcer is still a matter of controversy. In the present study, here reported from the Veterans Administration Center and the University of Southern California, Los Angeles, the authors investigated the relationship of peptic-ulcer pain to motility and *p*H level in the stomach and duodenum in 7 patients with active but uncomplicated duodenal ulcer, The method was as follows. A triple-lumen tube was passed under fluoroscopic control into the duodenum, one lumen being used for inflating a balloon which recorded duodenal motility on a recording oscillograph, the second for the periodic aspiration of duodenal contents, and the third lumen for the administration of N/10 hydrochloric acid. At the same time a double-lumen tube was introduced into the pyloric antrum, the two lumina in this case serving respectively to record motility and to aspirate gastric contents. The *p*H of the gastric and duodenal aspirates were determined with a Beckman *p*H meter.

Typical ulcer pain was produced in 4 out of the 7 patients when the duodenal *p*H was reduced to 1·88 by the introduction of N/10 HCl given at a rate of 180 drops per minute; surprisingly large quantities were required to reduce the *p*H of the duodenum—for example, in one patient 1,300 ml. of acid had to be infused to reduce the *p*H to 1·68. The onset of pain was not associated with any change in duodenal motility, and anticholinergic drugs which abolished motility did not relieve the pain. Pain was eased in all cases by aspiration of duodenal contents.

I. McLean Baird

391. **The Early Gastric Response to Irradiation. A Serial Biopsy Study**
M. B. GOLDGRABER, C. E. RUBIN, W. L. PALMER, R. L. DOBSON, and B. W. MASSEY. *Gastroenterology* [*Gastroenterology*] **27**, 1–20, July, 1954. 15 figs., bibliography.

The effect of *x* rays on the morphology of the gastric mucosa was studied by serial biopsy in 3 patients undergoing radiotherapy for duodenal ulcer at the University of Chicago Clinics. All were given a minimum depth dose of 1,600 r to the gastric fundus over 10 days through anterior and posterior portals measuring 170 sq. cm. at 250 kV and 25 mA, with 0·5 mm. Cu filter, F.S.D. 50 cm., and H.V.L. 1·5 mm. Cu. With this technique sickness is said to be minimal, and in these cases it was absent. Biopsy was carried out with the Wood suction biopsy tube, usually in the out-patient department.

Specimens of tissue were obtained from a man aged 69 with a 9-year history of duodenal ulcer on the 2nd, 8th, and 16th days after the start of treatment, then at weekly intervals up to the 8th week, and finally in the 16th week. The histological changes are described in great detail and photomicrographs are reproduced in colour. The patchy nature of the damage is particularly stressed, and the authors summarize their findings as follows. "The earliest change observed was coagulation necrosis of the depths of the fundal glands involving both chief and parietal cells. As this process progressed upwards the pits deepened and the neck cells proliferated. The necrotic tubules sloughed and were replaced in part by neck cells and partly by round cell infiltration. At the peak of the reaction there was partial to complete loss of glandular substance with mucosal thinning . . . and marked changes in the superficial epithelium. Reversion to normal was prompt and complete." The mucosa was normal on the 2nd day, the maximum change was seen at 3 weeks, and by 6 weeks there was considerable reversion to normal. The basal secretion of free acid before irradiation was 48 units, rising to 85 units after the injection of histamine. From the 2nd week onwards there was no acid in the basal secretion, but at 12 weeks there was a secretion of 30 units after histamine. In the other two patients, a man aged 34 with a 7-year history and a woman aged 58 with a 15-year history, the changes were less marked, and by 14 weeks recovery of secretion was rather more complete.

[This is, the abstracter believes, the most careful study of the effects of gastric irradiation so far made in man. It confirms that severe and extensive damage can be done to the gastric mucosa without causing symptoms. The wisdom or otherwise of the procedure is not discussed.] *Denys Jennings*

392. **Clinical and Experimental Studies with Banthine and Probanthine in Peptic Ulcer**
H. A. RAFSKY, H. D. FEIN, L. BRESLAW, and J. C. RAFSKY. *Gastroenterology* [*Gastroenterology*] **27**, 21–30, July, 1954. 9 refs.

A comparative investigation of the results obtained with drug therapy and conventional methods of treatment in patients with peptic ulcer is reported from the Lenox Hill Hospital, New York. Of 200 patients aged 26 to 75 years, 83 received "banthine" (methantheline), 60 "probanthine" (propantheline), and 57 conventional treatment. The trial was not a planned one, but all the patients had "more or less the same symptoms", and those with other than duodenal ulcers were fairly equally distributed in the 3 groups. In the whole series 180 patients had duodenal ulcer, 15 gastric ulcer, 2 gastric and duodenal ulcers, and 3 marginal ulcers. The period of observation ranged from 3 months to 2 years. All patients received a bland ulcer diet except during acute episodes, when a modified Sippy diet was given. In the 3 groups there were respectively 61, 41, and 33 patients with an ulcer crater, and the radiological findings in these patients after 2 to 6 weeks' treatment are tabulated as follows:

	Methantheline	Propantheline	Conventional Treatment
No ulcer crater	51	36	17
Ulcer crater smaller; patient asymptomatic	6	3	9
No change in ulcer crater; symptoms persisting	4	2	7

The authors were impressed by, but unable to explain, the dramatic and rapid relief of pain by the anticholinergic drugs. The dosages employed were sufficiently high to cause blurring of vision, but there was no "striking reduction in the acidity and gastric juice". The gastric emptying time was, however, definitely delayed. All patients with pyrosis were given alkalis, those receiving conventional therapy benefiting more than those given the two anticholinergic drugs. In a very few cases haemorrhage or perforation occurred while symptoms were under control. It is concluded that propantheline causes fewer side-effects than methantheline, that both drugs are to be preferred to atropine, and that administration of these drugs has advantages over conventional methods in the treatment of peptic ulcer. [No information is given concerning the incidence of relapse.] *Denys Jennings*

393. **Benign Ulcer of the Greater Curvature of the Stomach**
B. G. GRIFFIN. *Gastroenterology* [*Gastroenterology*] **27**, 178–182, Aug., 1954. 3 figs., 12 refs.

The author reports 3 cases of benign ulcer on the greater curvature of the stomach from the Lahey Clinic, Boston. In all 3 cases resection was carried out, and very careful histological examination showed no evidence of malignancy.

The literature concerning benign ulcers at this site is reviewed, only 32 such cases having previously been reported in which the benign nature of the ulcer was established with reasonable certainty. The 3 cases now reported were all seen during a single 12-month period. *T. D. Kellock*

Cardiovascular System

394. **Splitting of the First and Second Heart Sounds**
A. LEATHAM. *Lancet* [*Lancet*] **2**, 607–613, Sept. 25, 1954. 15 figs., 16 refs.

An auscultatory and phonocardiographic study of the heart sounds in health and disease is presented in this paper, which is based on experience at the London Hospital and the National Heart Hospital, London. Only those sounds which can be clearly heard are considered in detail.

Splitting of the first heart sound is found in most healthy people and is usually more easily heard during expiration. The second component of the split first sound is usually louder at the tricuspid area and occurs after the initial rise in pressure in the carotid artery. It is thought, therefore, that the first element is due to closure of the mitral valve and the second to closure of the tricuspid valve. The interval between the sounds is usually 0·02 to 0·03 second. Splitting of the first heart sound must be distinguished from the addition of an auricular sound, a presystolic murmur, and the early systolic click of a dilated pulmonary artery or ascending aorta. An added auricular sound preceding the first sound is of lower pitch, and is separated by a wider interval than is common with a split first sound. A presystolic murmur is loudest at the apex after exertion and is commonly accompanied by a loud first sound, an opening snap, and a mid-diastolic murmur. The early systolic click which sometimes accompanies dilatation of the pulmonary artery or the proximal aorta is sharp in quality and loudest at the base of the heart; it is heard at the apex only if very loud.

The second heart sound is normally split because of the slightly asynchronous contraction of the ventricles and earlier closure of the aortic valve. The interval between the two components is wider in inspiration (0·05 second) and may not be detectable in expiration. The gap between the aortic and pulmonary components of the second heart sound is unduly wide in the presence of pulmonary stenosis and of conduction delay due to right bundle-branch block. This wide splitting is best appreciated in expiration, during which the interval is normally very small or undetectable. A combination of an early pulmonary systolic sound and a widely split second sound suggests the presence of pulmonary stenosis; but wide splitting may also be due to early closure of the aortic valve in mitral incompetence. Conduction delay in left bundle-branch block may cause wide splitting due to very late closure of the aortic valve. This state of affairs can be recognized by the fact that the gap diminishes in inspiration when pulmonary valve closure is delayed. In pulmonary hypertension the second heart sound at the pulmonary area is loud, but splitting may be absent or the gap extremely small.

The third heart sound can usually be distinguished from the pulmonary component of a split second sound by its quality, site of maximum intensity, and behaviour during respiration. Its differentiation from an opening snap is important because of its completely different significance; in mitral valvular disease it indicates incompetence rather than stenosis.

[This paper is very concise and well illustrated and should be consulted in the original.]

D. W. Barritt

395. **Factors Contributing to Success or Failure in the Use of a Pump Oxygenator for Complete By-pass of the Heart and Lung, Experimental and Clinical**
G. H. A. CLOWES, W. E. NEVILLE, A. HOPKINS, J. ANZOLA, and F. A. SIMEONE. *Surgery* [*Surgery*] **36**, 557–579, Sept., 1954. 10 figs., 37 refs.

The use of a pump oxygenator for by-passing the heart and lungs is discussed in the light of 74 experiments on dogs in which the circulation was by-passed for 25 minutes or more. Of the 74 animals, 34 died; in 14 death was due to postoperative haemorrhage, and in 9, in which the blood pressure remained low, probably to brain damage, there being some evidence of such damage in the electroencephalogram. Other causes of death were minute fibrin emboli and bacterial infection from incomplete sterilization of the apparatus.

The apparatus was also used on 3 patients who were desperately ill, all of whom died. In one case a tumour inside the left auricle was removed in a dry operative field; the patient's blood pressure, however, remained low and she became anuric. At necropsy evidence of cerebral infarction was found. In the other 2 cases transient benefit was observed. *J. McMichael*

396. **A Study of the Serial Electrocardiographic Pattern Changes Occurring with Two Sequential Anterior Myocardial Infarctions**
H. A. FLACK, J. A. MART, and C. C. MAHER. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **228**, 288–297, Sept., 1954. 3 figs., 12 refs.

The authors present, from the Northwestern University Medical School and Passavant Memorial Hospital, Chicago, an analysis of the clinical and serial electrocardiographic records of 12 patients who had suffered two successive anterior myocardial infarctions. The interval between the infarctions ranged from 3 months to over 8 years, with an average of 2·9 years. In 3 cases there were no residual electrocardiographic defects as a result of the first attack. In the remainder there were persistent abnormalities: T_1 was inverted in one case and diphasic or of low voltage in 4, while the precordial T waves were inverted in one and diphasic or of low voltage in 8 cases. Significant Q waves were residual in only 2 records.

The pattern of the serial electrocardiographic changes of the second infarction were fundamentally similar to

those of the first, and stress is laid upon the fact that diagnosis of the second anterior infarction was dependent not only upon the electrocardiographic changes, but also upon a comparison of these with the clinical and electrocardiographic records obtained after the first infarction. In one of the 2 cases which came to necropsy, in which death occurred 12 hours after the second attack, there was evidence of both new and old infarctions; in the other, in which death occurred several years after the second attack, two separate scars could not be identified. The conclusion is therefore reached that in myocardial infarction " the exact clinico-pathologic status of any given patient necessitates a correlation of a careful chronologic medical history, serial electrocardiographic studies, and the pathologic report ".

William A. R. Thomson

397. **Myocardial Toxoplasmosis**
J. W. PAULLEY, R. JONES, W. P. D. GREEN, and E. P. KANE. *Lancet* [*Lancet*] **2**, 624–626, Sept. 25, 1954. 18 refs.

Three cases in which myocarditis was believed to be due to toxoplasmosis were seen at the East Suffolk and Ipswich Hospital in the 12 months ending June, 1954. It is suggested that toxoplasmosis should be considered as a possible aetiological factor in any case of myocarditis of unknown aetiology. The first patient, a mentally dull man, had a pleural effusion, recurrent hemiplegia, and an enlarged heart. The patient's serum was positive for toxoplasmosis by the dye test at 1 in 64 and by the complement-fixation test at 1 in 16. There was a strong family history of mental retardation and unexplained " myocarditis ". The other 2 patients had idiopathic cardiomegaly; the serum in one of these was positive for toxoplasmosis by the dye test at 1 in 32 and by the complement-fixation test at 1 in 16, and in the other at 1 in 512 and 1 in 32 respectively. A necropsy report on a sister of the first patient revealed " a non-specific myocarditis in the healing phase following severe focal necrosis ". Blood culture for *Toxoplasma* was negative.

The authors believe that these were cases of chronic toxoplasmosis, probably acquired rather than congenital.

E. G. Rees

398. **Antibiotic Therapy of Bacterial Endocarditis. VI. Subacute Enterococcal Endocarditis: Clinical, Pathologic and Therapeutic Consideration of 33 Cases**
J. E. GERACI and W. J. MARTIN. *Circulation* [*Circulation* (*N.Y.*)] **10**, 173–194, Aug., 1954. Bibliography.

During the first decade of treatment of bacterial endocarditis with antibiotics, 33 (approximately 10%) of the cases encountered at the Mayo Clinic were caused by enterococci (Lancefield's Group-D streptococci), which are highly resistant to penicillin. Endocarditis followed a urological procedure in 16 of the 33 cases, transurethral resection of the prostate accounting for 12 of these. In 15 cases there was no history of antecedent heart disease, while 2 patients had congenital, and the rest probably rheumatic, cardiac lesions. The usual clinical features were present, and major embolism occurred in 23 cases. Contrary to previous experience, renal damage was found at necropsy in all of the 6 cases in which it was performed, whereas abscesses were present (in the lungs) in only one.

The organisms isolated from the 31 treated patients were tested *in vitro* for sensitivity to various antibiotics, alone and in combination, by a bacteriostatic plate-dilution method, and in 5 cases the bactericidal effect of antibiotics added to active cultures was studied by means of survival counts. In each case the most effective combination was that of penicillin with dihydrostreptomycin. As a guide to dosage the serum concentrations of penicillin and dihydrostreptomycin were estimated in patients under treatment with these drugs, and in 3 cases the bactericidal effect of the patient's serum on the organism isolated was studied; it is concluded that the latter procedure is more valuable than the performance of sensitivity tests. Of 18 patients treated with penicillin alone, only 7 were cured, whereas of 12 patients given adequate doses of penicillin and dihydrostreptomycin, the infection was controlled in 10.

The authors recommend that for the first 6 weeks of treatment 1 g. of dihydrostreptomycin be given by intramuscular injection every 12 hours, together with aqueous benzylpenicillin by continuous intravenous drip infusion, starting with a daily dose of 10 mega units and increasing by 10 to 20 mega units daily until the serum is bactericidal in a dilution of 1 in 2 or 1 in 4. Probenecid may be used, if tolerated, to raise the blood penicillin level. It is also recommended that penicillin and dihydrostreptomycin should be given prophylactically to every patient, with or without evidence of a cardiac lesion, before, during, and after any urological operation.

[For full practical details of the recommended therapy and its bacteriological control the original paper should be consulted.] *D. Emslie-Smith*

CONGENITAL HEART DISEASE

399. **Isolated Valvular Pulmonic Stenosis. Clinical and Physiologic Response to Open Valvuloplasty**
S. G. BLOUNT, M. C. MCCORD, H. MUELLER, and H. SWAN. *Circulation* [*Circulation* (*N.Y.*)] **10**, 161–172, Aug., 1954. 8 figs., 15 refs.

During the last few years selected cases of pulmonary valvular stenosis have been treated by valvotomy with considerable clinical benefit. Most operations have been performed blindly by passing instruments through the right ventricle up to the valve, but a more deliberate and open approach has recently become possible by the application of hypothermia, which allows the circulation to be temporarily occluded while the pulmonary artery is opened and the valve incised under direct vision. This open procedure has undoubted advantages, against which should be balanced any additional risks introduced by the use of hypothermia.

The present authors used the blind method up to 1953 in a total of 8 cases, with 2 deaths. Since then they have performed the open operation under hypothermia on 7 occasions with no deaths. A detailed assessment of

the preoperative and postoperative condition in 5 cases from each group has been carried out and the results compared. The conclusion is reached that the open operation produces haemodynamic and physiological results greatly superior to those obtained by the earlier operation.

[This is an important paper which should be read in full by those interested in this branch of surgery.]

T. Holmes Sellors

400. **Repair of Atrial Septal Defects in Man under Direct Vision with the Aid of Hypothermia**

F. J. LEWIS, R. L. VARCO, and M. TAUFIC. *Surgery* [*Surgery*] **36**, 538–556, Sept., 1954. 7 figs., 17 refs.

The authors discuss some of the advantages and disadvantages of hypothermia in performing intracardiac operations, and stress the simplicity of the procedure in comparison with the setting up of an artificial circulation. They remark that when possible it is obviously better to repair atrial septal defects by direct vision, and report, from the University of Minnesota Medical School, 11 cases in which they were able to do this with the aid of hypothermia. They describe their technique in detail, and stress the importance of exploring the defect completely by palpation through the auricular appendage before the auricle is opened. Cooling was achieved by means of refrigerating blankets (illustrated) containing tubes through which a solution of alcohol at 25 F. (−4° C.) was run. The defects were, when possible, repaired with interrupted sutures.

Of the 11 patients, one died during the operation and one 3 days later of complete heart block, in another case the operation had to be abandoned because of fibrillation, but in 8 cases the septal defect was successfully sutured; in 5 of these cases postoperative cardiac catheterization showed no evidence of a shunt. Ventricular fibrillation occurred in 4 of the patients, but was easily controlled on each occasion. The authors state that the greatest hazard of the operation is erroneous preoperative diagnosis. In their opinion all adults who are suffering from atrial septal defect and who have symptoms should undergo this operation, and that when the operative risk has diminished still further probably all cases should be treated surgically.

J. R. Belcher

HEART FAILURE

401. **The Factor of Infection in Heart Failure**

F. J. FLINT. *British Medical Journal* [*Brit. med. J.*] 2, 1018–1022, Oct. 30, 1954. 5 figs., 13 refs.

Over a period of 12 months 300 patients were admitted to the City General Hospital, Sheffield, with congestive cardiac failure due to cor pulmonale (76 cases), rheumatic and non-specific valvular lesions (68 cases), ischaemic heart disease (65 cases), hypertensive heart disease (63 cases), or miscellaneous causes (28 cases). The incidence of heart failure was about twice as high in the winter as in the summer. Respiratory infection was the precipitating cause of failure in 156 cases (bronchitis in 103, pneumonia in 51, and tuberculosis in 2). In 11 other cases infection was of the aspiration type and was regarded as secondary, the patients being comatose or semicomatose.

Respiratory infection precipitated heart failure in 74 of the 76 patients with cor pulmonale, and in 82 of the 224 with other forms of heart disease. Post-mortem examination, which was permitted in 88 cases, showed that pneumonia was the cause of death in 21 and acute bronchitis in 17. The author discusses possible mechanisms whereby congestive heart failure is precipitated by respiratory infection, and stresses the importance of chemotherapy in addition to administration of digitalis and mersalyl in the management of these cases.

I. Ansell

402. **A Trial of Mercaptomerin in Severe Congestive Heart Failure**

W. D. ALEXANDER. *British Medical Journal* [*Brit. med. J.*] **2**, 391–393, Aug. 14, 1954. 2 figs., 9 refs.

The author, working at the Western Infirmary, Glasgow, has carried out a clinical trial of mercaptomerin (" thiomerin "), an organic mercurial diuretic which is sufficiently non-toxic to permit of subcutaneous administration. The urinary output of 6 patients with severe congestive heart failure was measured in the 48-hour periods following alternate injections of mercaptomerin and mersalyl. It was found that mercaptomerin by subcutaneous injection was at least as effective as mersalyl given by intramuscular injection. Only minor and infrequent local reactions were observed. *E. G. Rees*

403. **Observations on the Premonitory Syndrome of Chronic Cor Pulmonale in 49 Cases.** (Syndrome prémonitoire du cœur pulmonaire chronique. Quarante-neuf observations)

A. TOURNIAIRE, J. BLUM, F. DEYRIEUX, and M. TARTULIER. *Archives des maladies du cœur et des vaisseaux* [*Arch. Mal. Cœur*] **47**, 591–603, July, 1954. 4 figs., 27 refs.

The authors review their findings in 49 cases of chronic lung disease with evidence of early resultant cardiac involvement seen at the Hôpital Saint-Joseph, Lyons. All the patients were men and their mean age was 50 (range 37 to 70). The characteristic symptom was dyspnoea on effort, which caused a sense of stifling (*blocage thoracique*) in 30 cases but which passed off quickly on rest. In 6 cases it was accompanied by substernal pain of a constricting nature, radiating to the neck and shoulders but not to the arms. The authors believe the pain originated in the pulmonary artery [but they do not specifically mention the pulmonary arterial pressures found in these 6 cases]. The physical signs were cyanosis, emphysema, polycythaemia, and a raised haematocrit value; pulsation in the epigastrium in 28 cases was suggestive of right ventricular hypertrophy, and this finding was confirmed by fluoroscopy. The main branches of the pulmonary arteries were dilated but not unusually pulsatile. Electrocardiographic evidence of right ventricular hypertrophy was found only in a minority of cases. Cardiac catheterization revealed varying degrees of raised pressure in the pulmonary

artery; in the mildest cases this became evident only on effort. Studies of the haemodynamic and respiratory functions were also carried out.

A follow-up study of 24 of the patients showed progressive deterioration, resulting in death in 12 cases from right ventricular failure in an average period of 3 years. There was little change in 8 cases, but the remaining 4 showed a remarkable improvement in spite of the fact that there was little reduction in the pulmonary arterial pressure. In the management of such patients the authors stress the importance of avoidance of harmful conditions of climate and of work, and recommend prompt treatment of respiratory infections with antibiotics and, if necessary, rest in hospital and the administration of oxygen and aminophylline.

J. A. Cosh

CHRONIC VALVULAR DISEASES

404. **Rheumatic Heart-disease in Pregnancy**
M. MACLEOD. *Lancet* [*Lancet*] **2**, 668–671, Oct. 2, 1954. 20 refs.

It is pointed out that the effect of pregnancy on patients with mitral stenosis is to accentuate the natural features of the disease. The risk to life arises from acute pulmonary oedema and, to a lesser extent, from congestive heart failure. Early recognition of pulmonary hypertension and the efficient treatment of acute pulmonary oedema will contribute to a reduction in maternal mortality.

The author, writing from Aberdeen University, discusses his findings in 100 cases of rheumatic heart disease in pregnancy, in 83 of which there was mitral disease and in 17 mitral disease with aortic incompetence. Symptoms were classed as mild in 28 cases, moderate in 60, and severe in 12. Pregnancy was terminated in 6 of the patients with moderately severe symptoms and in 6 with severe symptoms. In the series as a whole there were 3 neonatal deaths and one stillbirth, but no maternal deaths. None of the patients was subjected to valvotomy. [This paper is of value because it indicates the results to be expected in these cases with expert obstetrical management in the absence of cardiac surgery.]

T. Semple

405. **A Study of Minute to Minute Changes of Arterio-venous Oxygen Content Difference, Oxygen Uptake and Cardiac Output and Rate of Achievement of a Steady State during Exercise in Rheumatic Heart Disease**
K. W. DONALD, J. M. BISHOP, and O. L. WADE. *Journal of Clinical Investigation* [*J. clin. Invest.*] **33**, 1146–1167, Aug., 1954. 9 figs., 8 refs.

The authors, from the Queen Elizabeth Hospital, Birmingham, describe a technique for measuring changes in venous and arterial blood oxygen saturation, and thus in cardiac output, during 5 minutes' exercise and subsequent recovery in patients with rheumatic heart disease. The errors of the method, which are discussed, were found not to be of significant importance. In over half of the cases studied a steady state—that is, no important change or trend—in oxygen uptake, arterio-venous oxygen difference, or cardiac output was observed after 2 or 3 minutes; in severe cases in which the cardiac output was not raised on exercise and there was an abnormally high arterio-venous oxygen difference a longer time was required to reach equilibrium. There appeared to be no correlation between the degree of dyspnoea and the ventilation, the level of mixed venous oxygen saturation, cardiac output, pulmonary arterial pressure, or pulmonary capillary pressure.

J. Shillingford

406. **Prevention of Systemic Arterial Embolism in Chronic Rheumatic Heart Disease by Means of Protracted Anticoagulant Therapy**
J. C. WOOD and H. L. CONN. *Circulation* [*Circulation (N.Y.)*] **10**, 517–523, Oct., 1954. 29 refs.

407. **Mitral Valve Disease over the Age of 50.** [In English]
F. J. HEBBERT and J. RANKIN. *Acta medica Scandinavica* [*Acta med. scand.*] **150**, 101–118, Oct. 2, 1954. 40 refs.

Rheumatic heart disease is more common in the older age groups than was at one time supposed, and in this paper from Stobhill Hospital, Glasgow, the authors review 106 cases of mitral valve disease occurring in patients (71 women and 35 men) aged 50 to over 80. In 75 cases the condition was diagnosed clinically; this diagnosis was confirmed at necropsy in 57 of the cases, but in 16 mitral valve disease was considered to have been either a slight or an inconsequent contributory factor in the symptomatology.

Of the 85 patients from whom a history of previous illnesses was obtained, 38 had had acute rheumatism or chorea at an average age of 22·5 years. The main presenting symptom was dyspnoea on exertion, which was often related to the onset of auricular fibrillation. The average duration of breathlessness was 5½ years. There was a history of multiple pregnancy in a number of cases—a total of 157 children having been born to 39 of the women in the series—indicating that uncomplicated mitral stenosis is not a contraindication to pregnancy and does not affect longevity. Hypertension—that is, a blood pressure exceeding 150/90 mm. Hg—was present in 38 of the cases.

The authors consider that the late onset of rheumatic infection and the freedom from recurrence are the most important factors in the longevity of these patients. They discuss the difficulty of diagnosing rheumatic mitral valve disease in old age, and emphasize that in many cases the condition may be regarded as benign.

P. D. Bedford

408. **Mitral Insufficiency: the Experimental Use of a Mobile Polyvinyl Sponge Prosthesis**
T. N. P. JOHNS and A. BLALOCK. *Annals of Surgery* [*Ann. Surg.*] **140**, 335–341, Sept., 1954. 8 figs., 15 refs.

The authors point out that the cause of mitral insufficiency is usually twofold: (1) immobility of the valve leaflets as a result of rheumatic inflammation; and

(2) enlargement of the valve ring as a result of dilatation of the left ventricle. Mild insufficiency is usually combined with marked mitral stenosis, and the regurgitant flow, though very noticeable, may be small. With the development of heart failure, however, the degree of insufficiency is far greater and stenosis no longer plays a prominent part.

A number of operations have been introduced in the attempt to remedy mitral insufficiency. The use of slings made of pericardium may help initially to improve the function of the valve, but they probably always atrophy. Prostheses made of plastic materials, which have the virtue of permanence, if nothing else, have also been used with varying success, the most promising method being to provide some form of baffle which, in ventricular systole, is thrust up into the orifice, but remains free to let blood pass from the auricle to the ventricle during diastole.

The authors describe a method by which a spindle-shaped polyvinyl-sponge prosthesis is introduced through the left auricle into the ventricle, where it is suspended across the mitral orifice between the commissures and parallel to the opposing edges of the leaflets. Its ends are pulled through the myocardium at the apices of the two papillary muscles and anchored to the epicardial surface of the heart. This technique has been developed in experiments on dogs with a normal mitral valve. In specimens obtained some time after the operation the prosthesis was covered by thin endocardium and there was little evidence of gross thrombosis. In one instance the plastic material has been tolerated within the heart for a year. *T. Holmes Sellors*

CORONARY DISEASE AND MYOCARDIAL INFARCTION

409. **The Relationship between Scapulo-humeral Periarthritis and Coronary Disease.** (Contributo allo studio dei rapporti tra periartrite scapolo-omerale e malattie delle coronarie)

G. P. VECCHI and V. RUBBIANI. *Minerva medica* [*Minerva med. (Torino)*] **2**, 755–759, Sept. 29, 1954. 25 refs.

The occurrence of pain and limitation of movement in the shoulder in patients suffering from coronary ischaemia is well recognized. In this paper from the University Medical Clinic, Modena, the authors describe 6 typical cases to illustrate the clinical features and report an attempt to determine whether patients complaining primarily of symptoms of scapulo-humeral periarthritis present any evidence of coronary insufficiency.

In a series of 48 such patients, ranging in age from 27 to 68, electrocardiography showed that 9 had definite evidence of coronary insufficiency, while a further 10 suffered from lesser degrees of myocardial damage. Few of these patients had symptoms referable to the cardiovascular system, but since the electrocardiogram was abnormal in nearly 40% of them it is suggested that the heart should be carefully investigated in all such cases. Two reasons are given for the association of these lesions: (1) the similarity of the sympathetic nerve supply to the shoulder and the heart; and (2) the fact that the connective tissue and vascular structures in the myocardium, shoulder, thyroid gland, and gall-bladder have a common developmental origin. As might be expected, therefore, periarthritis of the shoulder is also often associated with thyrotoxicosis and cholecystitis.

[Unfortunately, no comparable electrocardiographic findings are given for a group of patients of the same age distribution not suffering from scapulo-humeral periarthritis.] *A. Paton*

410. **Application of Induced Pulmonary Arterial Collateral Circulation as Collateral Supply to the Heart**

W. E. BLOOMER, H. STERN, and A. A. LIEBOW. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol. (N.Y.)*] **86**, 202–203, May, 1954. 1 fig., 13 refs.

The production of an artificial collateral circulation to the surface of the heart has been attempted in a number of ways. The present authors describe a method which they have applied in dogs in which they ligated the pulmonary artery and then produced fusion between the bare surfaces of the heart and lung by cauterizing their opposing surfaces with silver nitrate. Between 9 and 20 weeks after the operation vinylite plastic casts of the coronary and pulmonary vessels were made and showed that there was free communication between the two circulations.

The authors consider it probable that the blood flow initially is from the coronary arteries to lung, but are continuing their experiments to see whether this is reversed after the coronary circulation has been interrupted. *T. Holmes Sellors*

411. **The Physiologic Explanation of the Changes in the Coronary Circulation Precipitated by Aortic–Coronary Sinus Anastomosis**

A. A. BAKST, J. COSTAS-DURIEUX, H. GOLDBERG, and C. P. BAILEY. *Journal of Clinical Investigation* [*J. clin. Invest.*] **33**, 1329–1337, Oct., 1954. 3 figs., 12 refs.

412. **Intravenous Trypsin in Experimental Myocardial Infarction**

C. M. AGRESS, H. I. JACOBS, M. J. BINDER, W. G. CLARK, L. KAPLAN, M. LEDERER, and H. F. GLASSNER. *Circulation Research* [*Circulat. Res.*] **2**, 397–404, Sept., 1954. 5 figs., 9 refs.

The results obtained with trypsin in experimental coronary arterial embolism are described in this paper from the Veterans Administration Center and University of California, Los Angeles. Coronary occlusion was induced in 29 dogs by direct introduction of fibrin particles into the coronary artery, a double-lumen steel catheter being passed through the carotid artery. Evidence of resulting myocardial infarction was obtained by electrocardiography. In 13 dogs examination 8 days later showed extensive myocardial infarction, functionally occluded coronary arteries, and, microscopically, complete blockage of embolized vessels by fibrin particles interspersed with dense organizing thrombus

derived from the host. Intravenous infusions of crystalline trypsin in normal saline were given to 16 animals during the 8 days following coronary occlusion, the dosage ranging in different dogs from a single infusion of 25,000 units to 6 successive infusions each of 250,000 units. Mild to massive infarction was found in these 16 animals at necropsy on the eighth day, but unlike the findings in the 13 untreated animals perfusion of the coronary arteries gave a free flow of perfusate past the embolus. Histological examination showed that this was due to entire absence of host thrombus, although the fibrin thrombi themselves were unaffected. No evidence of proteolysis was found in the infarcted tissue or in the vascular endothelium. In 2 healthy dogs given large doses of trypsin no damage was found in any organ on macroscopic and histological examination. The authors believe that administration of a proteolytic agent such as trypsin can aid the dissolution of a coronary arterial thrombus without further damage to the infarcted myocardium. *Bernard Isaacs*

See also Pathology, Abstract 304.

DISTURBANCES OF RHYTHM AND CONDUCTION

413. **Right Ventricular Block. A Clinical Study of 232 Cases.** (Les blocks intraventriculaires droits. Étude clinique de 232 cas)
G. FISCHER, M. M. VASTESAEGER, and P. VANDERSTRAETEN. *Acta clinica Belgica* [*Acta clin. belg.*] **9**, 230–261, May–June, 1954. 12 figs., bibliography.

The authors present, from the Medico-chirurgical Institute, Ixelles, Belgium, a clinical study of 232 cases of right ventricular block, comprising 130 cases from private practice and 102 from three hospitals, 72% of the patients being male and 28% female. In the youngest patients the lesion was of congenital aetiology only and all these patients showed minor (incomplete) degrees of block (QRS complex of 0·10 to 0·12 second). The patients in the age group 20 to 40, almost exclusively male, included 45% of cases of unknown aetiology. By relating these to the figures for proven cases of coronary atherosclerosis the authors contend that this disease is in fact the cause of block in such cases, and occurs at an earlier age in men than in women; in this group, 81% of cases were attributed to coronary disease. Of 40 cases presenting only minor degrees of block—this small proportion is attributed to very strict selection—17 (42%) were due to incontestable coronary arterial disease and 10 (25%) were of unknown aetiology. With increasing age the proportion of cases of minor block diminished.

In discussing the development of block in cases of cor pulmonale and mitral stenosis the authors observe that the majority of these patients are aged over 40 and possibly subject to the additional factor of coronary disease. They cite several cases of cardiac infarction and coronary sclerosis to support their belief that damage to an area of myocardium without damage to the bundle of His can cause block, whereas considerable interference with the bundle of His may occur without block. The authors suggest that, apart from the factor of infection in acute rheumatism, the sole determinant of right ventricular block is myocardial ischaemia, whether relative (as in ventricular hypertrophy), in which case it leads to a minor degree of block, or absolute, leading to major degrees of block. *R. S. Stevens*

414. **The Dynamics of the Heart in Complete A-V Block. An Angiocardiographic Study**
J. LIND, C. WEGELIUS, and H. LICHTENSTEIN. *Circulation* [*Circulation* (*N.Y.*)] **10**, 195–200, Aug., 1954. 1 fig., 3 refs.

Using rapid biplane angiocardiography with simultaneous electrocardiography the authors, working at the Karolinska Institute and Norrtulls Hospital, Stockholm, studied circulatory dynamics in the great veins, right atrium, right ventricle, and pulmonary artery in a patient aged 3 years with complete atrio-ventricular block. The following conclusions are reached from their observations.

When atrial systole occurs immediately after the T wave in the electrocardiogram the ventricle is empty and so the atrium empties well, whereas later in ventricular diastole atrial emptying is less complete. A second atrial systole during ventricular diastole fails to push blood into the filled ventricle and regurgitation occurs into the inferior vena cava. Atrial systole occurring during ventricular systole forces blood into all the afferent veins. Diastolic filling of the ventricle is much faster than systolic emptying, even without atrial systole, while great but transient functional dilatation of the pulmonary artery occurs during ventricular systole. This description applies equally to the left side of the heart.

[These points are well illustrated by 28 very clear angiocardiograms correlated with a marked electrocardiogram.] *D. Emslie-Smith*

BLOOD VESSELS

415. **Treatment of Venous Thrombosis with Anticoagulants. Review of 1135 Cases**
J. MARKS, B. M. TRUSCOTT, and J. F. R. WITHYCOMBE. *Lancet* [*Lancet*] **2**, 787–791, Oct. 16, 1954. 3 figs., 6 refs.

In the Cambridge area during the past 5 years 1,135 patients with superficial and deep peripheral venous thrombosis have been treated with anticoagulant drugs. The regimen used was the administration, as soon as the diagnosis was made, of ethyl biscoumacetate, 1·2 g., or phenylindanedione, 250 mg. by mouth, and the intramuscular injection of heparin, 150 mg., with hyaluronidase, 0·1 mg. This was followed by heparin in a dose of 50 mg. combined with 0·1 mg. hyaluronidase 4-hourly for four doses only. Subsequent dosage with phenylindanedione or ethyl biscoumacetate was regulated by the trend in the level of the prothrombin time as estimated by a modified Quick one-stage technique. Bed rest and splinting were advised for patients with pain, but active exercises in bed were encouraged as soon as pain sub-

sided. On the average, patients attained freedom from pain in 18 hours in cases of superficial venous thrombosis and in 3 to 4 days in those of deep thrombosis, while the average stay in bed was 3 to 5 days in the former and 5 to 7 days in the latter. Haemorrhagic incidents were rare, and it was possible to treat 307 of the patients in their own homes without the occurrence of untoward side-reactions. Three patients died while undergoing anticoagulant therapy, all from pulmonary embolism. In the 5-year period of the study, despite vigilance in the early diagnosis and treatment of venous thrombosis in the leg, 54 cases of sudden, unheralded, fatal pulmonary embolism occurred among patients who were not receiving anticoagulants.

The authors conclude that the morbidity and mortality of peripheral venous thrombosis can be materially reduced by anticoagulant therapy, but the incidence of fatal, unheralded pulmonary embolism remains uninfluenced. *Bernard Isaacs*

416. **Additional Observations Concerning the Physiology of the Hypertension Associated with Experimental Coarctation of the Aorta**
H. W. Scott, H. A. Collins, A. M. Langa, and N. S. Olsen. *Surgery* [*Surgery*] **36**, 445–459, Sept., 1954. 7 figs., 33 refs.

In experiments carried out on 97 dogs at Vanderbilt University School of Medicine, Nashville, Tennessee, the carotid and femoral blood pressure was first measured periodically during 7 to 30 days by direct puncture of these arteries, after which aortic coarctation was produced either by bridging the gap in a divided aorta by anastomizing the cut end of the left subclavian artery to the distal portion of the aorta, or by excising part of the wall of the aorta and suturing the cut edges together to produce aortic narrowing. It was found that to produce hypertension the coarctation must reduce the diameter of the aorta by 60 to 80%.

Observation showed that a coarctation above the origin of the renal arteries was followed, after a latent interval of 4 to 5 days, by a gradual increase in carotid arterial pressure, the mean femoral arterial pressure, after an initial depression, also being increased. Constriction of the aortic isthmus was followed by an immediate rise in blood pressure, but this disappeared within 4 to 5 hours to give way to the gradual development of hypertension. The acute hypertension was therefore considered to be mechanical in origin. The chronic hypertension following coarctation of the aorta, however, is considered to be intimately concerned with the blood supply to the kidneys, since it occurred only if the aortic constriction was above the origin of the renal arteries and was great enough severely to restrict renal blood supply, and did not arise if the aortic constriction was below the origin of the renal arteries. Further experiments showed that the hypertension regressed when one kidney was transplanted so that its blood supply was derived from the aorta above the site of constriction, although this occurred only if the remaining kidney was removed; moreover, regression of the hypertension did not occur if the transplanted kidney derived its blood supply from vessels below the constriction. There was also no demonstrable change in the level of brachiocephalic blood pressure when the aorta was compressed or even completely severed below the origin of the renal arteries. Bio-assay of renal venous blood of some of the animals rendered hypertensive in this manner seemed to suggest that a pressor substance, " phirentasin ", was circulating in the blood and that this disappeared when the hypertension regressed. It is concluded that these experiments confirm that the kidneys are intimately concerned in the production and maintenance of the hypertension associated with coarctation of the aorta. *H. E. Holling*

SYSTEMIC CIRCULATORY DISORDERS

417. **The Effect of Weight Reduction upon the Blood-pressure of Obese Hypertensive Women**
A. P. Fletcher. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **23**, 331–345, July, 1954. 2 figs., 37 refs.

Weight reduction was found to lower the blood pressure of a group of obese hypertensive women studied at St. Mary's Hospital, London, whereas the blood pressure did not fall significantly in a comparable series of obese hypertensive women who failed to lose weight. Although the blood pressure was measured by the cuff method, the experiment was designed to eliminate error due to reduction of arm girth, and the conclusion appears to be valid that obesity had been of aetiological importance in the former group. *Paul Wood*

418. **Studies on the Control of Hypertension by Hyphex. V. Effects on the Course of the Malignant Stage**
H. A. Schroeder, J. D. Morrow, and H. M. Perry. *Circulation* [*Circulation (N.Y.)*] **10**, 321–330, Sept., 1954. 4 figs., 12 refs.

Hexamethonium chloride and " hyphex " (1-hydrazinophthalazine) were given by mouth to 106 patients in the malignant phase of hypertension who were seen at Barnes Hospital, St. Louis, Missouri, during the 2-year period beginning August, 1951. Criteria for clinical recognition of malignant hypertension included a high, fixed diastolic pressure, diminished renal function, proteinuria, hypertensive retinopathy with papilloedema, and other signs of rapid deterioration. Of the 106 patients, however, 24 were considered to have " early malignant " hypertension, and in 14 of these frank papilloedema was absent, though retinal haemorrhage and exudates were observed. Some degree of renal failure was present in 43, while 10 others were frankly uraemic.

For various reasons 25 patients discontinued both drugs and 3 discontinued hexamethonium; of these 28 patients, 25 had died by August, 1954, the 3 surviving patients being in the group with early malignant hypertension. The 10 patients with uraemia died during the initial period in hospital, having derived no benefit from treatment. Of the remaining 68 patients, 14 died while under treatment, some from causes such as carcinoma of the lung, pneumonia, and postoperative shock, though in 4 cases death was due to acute interstitial

Haematology

423. **Hormonal Factors Influencing Erythropoiesis.** [In English]
D. C. Van Dyke, A. N. Contopoulos, B. S. Williams, M. E. Simpson, J. H. Lawrence, and H. M. Evans. *Acta haematologica* [*Acta haemat.* (*Basel*)] **11**, 203–222, April, 1954. 1 fig., bibliography.

The regulatory mechanism which maintains the number and volume of circulating erythrocytes at a constant level is not yet fully understood, though the rate of erythropoiesis is apparently determined by the oxygen saturation of the tissues. Cross-transfusion and parabiotic experiments in animals, however, have suggested that hormonal substances may be of importance in controlling erythropoiesis. In order to determine which of the endocrine organs is involved the authors, working at the University of California, studied the effects of removal of pituitary, adrenal, and thyroid glands and of the testes on the blood picture of different groups of rats. The total circulating erythrocyte volume was determined by the labelled-cell dilution method with radioactive iron (^{59}Fe) and the haemoglobin concentration by the Turner method. When anaemia developed the animals were first exposed to low oxygen tensions to discover whether their erythropoietic tissues would respond, and then treated with the active principle of the gland which had been removed. The haematological findings in each group of animals, together with control observations, are clearly tabulated.

By these means it was shown that the removal of the thyroid and adrenal glands and the gonads, either individually or in combination, produced mild anaemia but did not affect the erythropoietic response to anoxaemia. Replacement therapy, moreover, did not produce polycythaemia, though it corrected any anaemia. Hypophysectomized rats, on the other hand, developed a severe anaemia and their erythropoietic response on exposure to low oxygen tensions was impaired. It was also found that the oral administration of the anterior lobe of the sheep's pituitary gland not only repaired the anaemia in hypophysectomized animals, but also caused polycythaemia in normal controls and in adrenalectomized animals without stimulating the thyroid glands or testes or increasing the rate of growth. It was therefore concluded that the anterior pituitary gland produces a hormone which acts directly on the bone marrow and is concerned with the regulation of the rate of erythropoiesis.

H. Payling Wright

424. **Investigation of Leukocyte Agglutination in Serum of Compatible and Incompatible Blood Groups.** [In English]
S. Moeschlin and E. Schmid. *Acta haematologica* [*Acta haemat.* (*Basel*)] **11**, 241–250, April, 1954. 4 figs., 25 refs.

Following the discovery of a leucocyte agglutinin in the serum and plasma in cases of amidopyrine agranulocytosis (Moeschlin and Wagner, *Acta haemat.* (*Basel*), 1952, **8**, 29; *Abstracts of World Medicine*, 1952, **12**, 566) the authors, working at the University of Zürich, have investigated the occurrence of agglutination on the addition of serum of compatible and incompatible blood groups to a suspension of leucocytes isolated by the technique of Robineaux and Debrun. Blood was obtained from 30 donors, and 380 different leucocyte-serum combinations tested. Out of the 174 combinations in which there was ABO or Rh incompatibility, only in 60 could leucocyte agglutination be demonstrated; of the remaining 206 combinations, leucocyte agglutination occurred in 10. Leucocyte agglutination was attributable in the majority (97%) of cases to the group specific isoagglutinins, but the probable presence in the remaining 3% of non-specific agglutinins may well explain, on an allergic basis, the occurrence of certain agranulocytotic and leucopenic conditions.

H. Payling Wright

425. **The Isolation and Properties of Substances of Human Origin Possessing Blood-group B Specificity**
R. A. Gibbons and W. T. J. Morgan. *Biochemical Journal* [*Biochem. J.*] **57**, 283–295, 1954. 5 figs., 36 refs.

426. **The Indications for Splenectomy in Osler's Disease [Subacute Bacterial Endocarditis].** (Indications de la splénectomie dans la maladie d'Osler)
G. Giraud, P. Cazal, H. Latour, A. Lévy, and P. Puech. *Archives des maladies du cœur et des vaisseaux* [*Arch. Mal. Cœur*] **47**, 410–416, May, 1954. 9 refs.

In some apparently healed cases of subacute bacterial endocarditis (here given its eponymic name of Osler's disease) there later occur recrudescence of the fever and enlargement of the spleen. Splenectomy, proposed by Riesman in 1918 (*J. Amer. med. Ass.*, 1918, **71**, 10) proved at that time too hazardous an undertaking to be generally accepted, but since the advent of penicillin the authors believe the operation is worthy of reconsideration. With this in mind they have removed the spleen in 3 cases of subacute bacterial endocarditis, in one of which there was a massive splenic infarct and in two others persistent splenomegaly after relapse following antibiotic therapy. In all 3 cases the result is described as " satisfactory ".

The authors suggest that the operation is justified on the following grounds. When massive infarction of the spleen occurs in this disease there is always the possibility of suppuration of the infarct and its eventual rupture into the peritoneal cavity. It is also claimed that organisms in the splenic sinuses are relatively inaccessible to attack by antibiotics and may be the cause of relapse after cessation of treatment of the cardiac condition. In 2 of the cases described streptococci were recovered from the spleen, although cultures of the blood and bone marrow had been sterile.

P. C. Reynell

ANAEMIA

427. **Hereditary Nonspherocytic Hemolytic Disease. A Study of a Singular Familial Hemolytic Syndrome**
A. G. MOTULSKY, W. H. CROSBY, and H. RAPPAPORT. *Blood* [*Blood*] **9**, 749–772, Aug., 1954. 8 figs., bibliography.

In this paper are described the thorough haematological studies carried out at the Walter Reed Army Medical Center and Armed Forces Institute of Pathology, Washington, D.C., on 4 patients, belonging to 3 families, who suffered from hereditary non-spherocytic haemolytic disease. This disorder differs haematologically and clinically from the better-known hereditary haemolytic anaemias in that there are no striking or consistent morphological abnormalities of the erythrocytes. From hereditary spherocytosis it is distinguished by the regular absence of spherocytosis and increased fragility of the erythrocytes, by the usually less rapid autohaemolysis on incubation, and by a less marked increase in osmotic fragility of the cells on incubation. Clinically, the disorder is distinguished from hereditary spherocytosis chiefly by the fact that splenectomy has little or no beneficial effect—this the present authors link with the different histology of the spleen in the two conditions, the striking congestion with blood which is a characteristic finding in hereditary spherocytosis being absent in the non-spherocytic type.

Haemolysis in hereditary non-spherocytic haemolytic disease appears to be due to a basic defect in the erythrocytes, the nature of which is unknown. The disorder is probably transmitted through a Mendelian dominant gene which, however, may sometimes be of low expressivity.

The literature is reviewed and the differential diagnosis is discussed. The authors conclude from various clinical and haematological differences between the cases described that several distinct types of hereditary nonspherocytic haemolytic disease may exist.

J. V. Dacie

428. **The Combined Study of Agglutination, Hemolysis and Erythrophagocytosis. With Special Reference to Acquired Hemolytic Anemia**
J. A. BONNIN and L. SCHWARTZ. *Blood* [*Blood*] **9**, 773–788, Aug., 1954. 1 fig., 49 refs.

At the Postgraduate Medical School of London the authors investigated sera containing nine different types of haemagglutinating and haemolytic antibody. A technique employing suspensions of living human leucocytes was evolved by which it was possible to measure the power of a serum to promote haemagglutination, haemolysis, and erythrophagocytosis under varying conditions of temperature and *p*H, with and without previous heat-inactivation of the serum. Normal and trypsinized erythrocytes and erythrocytes from cases of paroxysmal nocturnal haemoglobinuria were used.

Only those sera which were potentially haemolytic were found to cause erythrophagocytosis, the phagocytic titre usually exceeding the haemolytic titre. Monocytes appeared to be more actively phagocytic than polymorphonuclear leucocytes. Except with the immune type of anti-A serum, phagocytosis did not occur if the serum had been inactivated by heat; in most instances, therefore, anti-erythrocytic antibodies require the presence of some heat-labile factor or factors before phagocytosis will take place. Haemolysis produced by systems other than antibody and complement—such as osmotic haemolysis or the lysis by acidified normal serum of the erythrocytes of paroxysmal nocturnal haemoglobinuria—was unaccompanied by phagocytosis. *J. V. Dacie*

429. **ABO Heterospecific Pregnancy and Hemolytic Disease. A Study of Normal and Pathologic Variants. I. Patterns of Maternal A and B Isoantibodies in Unselected Pregnancies**
W. W. ZUELZER and E. KAPLAN. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **88**, 158–178, Aug., 1954. 4 figs., 13 refs.

In 20 to 25% of all pregnancies the foetal erythrocytes possess an agglutinogen, A or B, not present in the mother's erythrocytes and to which her serum contains the corresponding antibody. The mechanisms which normally protect the foetus against the potentially harmful effects of the maternal isoantibodies and the cause of ABO haemolytic disease in a few cases are incompletely understood. The authors therefore studied the isoantibody pattern in 224 women, chiefly negro and of Group O, and their newborn babies. No difference in isoantibody pattern was found between homospecific and heterospecific pregnancies, although occasionally in heterospecific cases an immune response occurred in the puerperium. Such a response occurred only where the baby was a secretor and, if the baby belonged to Group A, only where the baby was of Subgroup A_1. A nonspecific response of the opposite antibody frequently also occurred. These responses apparently subside and do not affect the outcome of a subsequent pregnancy.

John Murray

430. **ABO Heterospecific Pregnancy and Hemolytic Disease. A Study of Normal and Pathologic Variants. II. Patterns of A and B Isoantibodies in the Cord Blood of Normal Infants**
W. W. ZUELZER and E. KAPLAN. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **88**, 179–192, Aug., 1954. 2 figs., 4 refs.

In continuation of the investigation reported above [see Abstract 429] the cord blood of 69 babies was examined and the isoantibody content compared with that of the mother. In the majority of cases the cord-blood serum of Group-O infants of Group-O mothers contained anti-A and anti-B antibodies. "Saline" agglutinins appeared in the cord-blood sera independently of the conglutinins. In heterospecific pregnancies, however, the heterologous antibody was found in the cord-blood serum, whereas the saline antibody antagonistic to the foetal erythrocytes was absent.

The authors conclude that the placenta is normally permeable to the maternal antibodies against A and B, but that A or B substances in the tissues of the foetus

Haematology

423. **Hormonal Factors Influencing Erythropoiesis.** [In English]
D. C. VAN DYKE, A. N. CONTOPOULOS, B. S. WILLIAMS, M. E. SIMPSON, J. H. LAWRENCE, and H. M. EVANS. *Acta haematologica* [*Acta haemat.* (*Basel*)] **11**, 203–222, April, 1954. 1 fig., bibliography.

The regulatory mechanism which maintains the number and volume of circulating erythrocytes at a constant level is not yet fully understood, though the rate of erythropoiesis is apparently determined by the oxygen saturation of the tissues. Cross-transfusion and parabiotic experiments in animals, however, have suggested that hormonal substances may be of importance in controlling erythropoiesis. In order to determine which of the endocrine organs is involved the authors, working at the University of California, studied the effects of removal of pituitary, adrenal, and thyroid glands and of the testes on the blood picture of different groups of rats. The total circulating erythrocyte volume was determined by the labelled-cell dilution method with radioactive iron (^{59}Fe) and the haemoglobin concentration by the Turner method. When anaemia developed the animals were first exposed to low oxygen tensions to discover whether their erythropoietic tissues would respond, and then treated with the active principle of the gland which had been removed. The haematological findings in each group of animals, together with control observations, are clearly tabulated.

By these means it was shown that the removal of the thyroid and adrenal glands and the gonads, either individually or in combination, produced mild anaemia but did not affect the erythropoietic response to anoxaemia. Replacement therapy, moreover, did not produce polycythaemia, though it corrected any anaemia. Hypophysectomized rats, on the other hand, developed a severe anaemia and their erythropoietic response on exposure to low oxygen tensions was impaired. It was also found that the oral administration of the anterior lobe of the sheep's pituitary gland not only repaired the anaemia in hypophysectomized animals, but also caused polycythaemia in normal controls and in adrenalectomized animals without stimulating the thyroid glands or testes or increasing the rate of growth. It was therefore concluded that the anterior pituitary gland produces a hormone which acts directly on the bone marrow and is concerned with the regulation of the rate of erythropoiesis. *H. Payling Wright*

424. **Investigation of Leukocyte Agglutination in Serum of Compatible and Incompatible Blood Groups.** [In English]
S. MOESCHLIN and E. SCHMID. *Acta haematologica* [*Acta haemat.* (*Basel*)] **11**, 241–250, April, 1954. 4 figs., 25 refs.

Following the discovery of a leucocyte agglutinin in the serum and plasma in cases of amidopyrine agranulocytosis (Moeschlin and Wagner, *Acta haemat.* (*Basel*), 1952, **8**, 29; *Abstracts of World Medicine*, 1952, **12**, 566) the authors, working at the University of Zürich, have investigated the occurrence of agglutination on the addition of serum of compatible and incompatible blood groups to a suspension of leucocytes isolated by the technique of Robineaux and Debrun. Blood was obtained from 30 donors, and 380 different leucocyte-serum combinations tested. Out of the 174 combinations in which there was ABO or Rh incompatibility, only in 60 could leucocyte agglutination be demonstrated; of the remaining 206 combinations, leucocyte agglutination occurred in 10. Leucocyte agglutination was attributable in the majority (97%) of cases to the group specific isoagglutinins, but the probable presence in the remaining 3% of non-specific agglutinins may well explain, on an allergic basis, the occurrence of certain agranulocytotic and leucopenic conditions.
H. Payling Wright

425. **The Isolation and Properties of Substances of Human Origin Possessing Blood-group B Specificity**
R. A. GIBBONS and W. T. J. MORGAN. *Biochemical Journal* [*Biochem. J.*] **57**, 283–295, 1954. 5 figs., 36 refs.

426. **The Indications for Splenectomy in Osler's Disease [Subacute Bacterial Endocarditis].** (Indications de la splénectomie dans la maladie d'Osler)
G. GIRAUD, P. CAZAL, H. LATOUR, A. LÉVY, and P. PUECH. *Archives des maladies du cœur et des vaisseaux* [*Arch. Mal. Cœur*] **47**, 410–416, May, 1954. 9 refs.

In some apparently healed cases of subacute bacterial endocarditis (here given its eponymic name of Osler's disease) there later occur recrudescence of the fever and enlargement of the spleen. Splenectomy, proposed by Riesman in 1918 (*J. Amer. med. Ass.*, 1918, **71**, 10) proved at that time too hazardous an undertaking to be generally accepted, but since the advent of penicillin the authors believe the operation is worthy of reconsideration. With this in mind they have removed the spleen in 3 cases of subacute bacterial endocarditis, in one of which there was a massive splenic infarct and in two others persistent splenomegaly after relapse following antibiotic therapy. In all 3 cases the result is described as " satisfactory ".

The authors suggest that the operation is justified on the following grounds. When massive infarction of the spleen occurs in this disease there is always the possibility of suppuration of the infarct and its eventual rupture into the peritoneal cavity. It is also claimed that organisms in the splenic sinuses are relatively inaccessible to attack by antibiotics and may be the cause of relapse after cessation of treatment of the cardiac condition. In 2 of the cases described streptococci were recovered from the spleen, although cultures of the blood and bone marrow had been sterile. *P. C. Reynell*

ANAEMIA

427. **Hereditary Nonspherocytic Hemolytic Disease. A Study of a Singular Familial Hemolytic Syndrome**
A. G. MOTULSKY, W. H. CROSBY, and H. RAPPAPORT. *Blood* [*Blood*] **9**, 749–772, Aug., 1954. 8 figs., bibliography.

In this paper are described the thorough haematological studies carried out at the Walter Reed Army Medical Center and Armed Forces Institute of Pathology, Washington, D.C., on 4 patients, belonging to 3 families, who suffered from hereditary non-spherocytic haemolytic disease. This disorder differs haematologically and clinically from the better-known hereditary haemolytic anaemias in that there are no striking or consistent morphological abnormalities of the erythrocytes. From hereditary spherocytosis it is distinguished by the regular absence of spherocytosis and increased fragility of the erythrocytes, by the usually less rapid autohaemolysis on incubation, and by a less marked increase in osmotic fragility of the cells on incubation. Clinically, the disorder is distinguished from hereditary spherocytosis chiefly by the fact that splenectomy has little or no beneficial effect—this the present authors link with the different histology of the spleen in the two conditions, the striking congestion with blood which is a characteristic finding in hereditary spherocytosis being absent in the non-spherocytic type.

Haemolysis in hereditary non-spherocytic haemolytic disease appears to be due to a basic defect in the erythrocytes, the nature of which is unknown. The disorder is probably transmitted through a Mendelian dominant gene which, however, may sometimes be of low expressivity.

The literature is reviewed and the differential diagnosis is discussed. The authors conclude from various clinical and haematological differences between the cases described that several distinct types of hereditary non-spherocytic haemolytic disease may exist.

J. V. Dacie

428. **The Combined Study of Agglutination, Hemolysis and Erythrophagocytosis. With Special Reference to Acquired Hemolytic Anemia**
J. A. BONNIN and L. SCHWARTZ. *Blood* [*Blood*] **9**, 773–788, Aug., 1954. 1 fig., 49 refs.

At the Postgraduate Medical School of London the authors investigated sera containing nine different types of haemagglutinating and haemolytic antibody. A technique employing suspensions of living human leucocytes was evolved by which it was possible to measure the power of a serum to promote haemagglutination, haemolysis, and erythrophagocytosis under varying conditions of temperature and *p*H, with and without previous heat-inactivation of the serum. Normal and trypsinized erythrocytes and erythrocytes from cases of paroxysmal nocturnal haemoglobinuria were used.

Only those sera which were potentially haemolytic were found to cause erythrophagocytosis, the phagocytic titre usually exceeding the haemolytic titre. Monocytes appeared to be more actively phagocytic than polymorphonuclear leucocytes. Except with the immune type of anti-A serum, phagocytosis did not occur if the serum had been inactivated by heat; in most instances, therefore, anti-erythrocytic antibodies require the presence of some heat-labile factor or factors before phagocytosis will take place. Haemolysis produced by systems other than antibody and complement—such as osmotic haemolysis or the lysis by acidified normal serum of the erythrocytes of paroxysmal nocturnal haemoglobinuria—was unaccompanied by phagocytosis. *J. V. Dacie*

429. **ABO Heterospecific Pregnancy and Hemolytic Disease. A Study of Normal and Pathologic Variants. I. Patterns of Maternal A and B Isoantibodies in Unselected Pregnancies**
W. W. ZUELZER and E. KAPLAN. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **88**, 158–178, Aug., 1954. 4 figs., 13 refs.

In 20 to 25% of all pregnancies the foetal erythrocytes possess an agglutinogen, A or B, not present in the mother's erythrocytes and to which her serum contains the corresponding antibody. The mechanisms which normally protect the foetus against the potentially harmful effects of the maternal isoantibodies and the cause of ABO haemolytic disease in a few cases are incompletely understood. The authors therefore studied the isoantibody pattern in 224 women, chiefly negro and of Group O, and their newborn babies. No difference in isoantibody pattern was found between homospecific and heterospecific pregnancies, although occasionally in heterospecific cases an immune response occurred in the puerperium. Such a response occurred only where the baby was a secretor and, if the baby belonged to Group A, only where the baby was of Subgroup A_1. A nonspecific response of the opposite antibody frequently also occurred. These responses apparently subside and do not affect the outcome of a subsequent pregnancy.

John Murray

430. **ABO Heterospecific Pregnancy and Hemolytic Disease. A Study of Normal and Pathologic Variants. II. Patterns of A and B Isoantibodies in the Cord Blood of Normal Infants**
W. W. ZUELZER and E. KAPLAN. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **88**, 179–192, Aug., 1954. 2 figs., 4 refs.

In continuation of the investigation reported above [see Abstract 429] the cord blood of 69 babies was examined and the isoantibody content compared with that of the mother. In the majority of cases the cord-blood serum of Group-O infants of Group-O mothers contained anti-A and anti-B antibodies. "Saline" agglutinins appeared in the cord-blood sera independently of the conglutinins. In heterospecific pregnancies, however, the heterologous antibody was found in the cord-blood serum, whereas the saline antibody antagonistic to the foetal erythrocytes was absent.

The authors conclude that the placenta is normally permeable to the maternal antibodies against A and B, but that A or B substances in the tissues of the foetus

neutralize the potentially harmful antibodies in heterospecific pregnancy. They found no evidence that secretion of A or B substances in the saliva had any protective value. There were a few cases where the baby was of Subgroup A_2 and the cord blood contained "saline" anti-A agglutinin. It was presumed that the latter antibody had the specificity anti-A_1 and therefore was not neutralized by the infant's tissues.

John Murray

431. **Clinical Features of the Genetic Variants of Sickle Cell Disease**
E. W. SMITH and C. L. CONLEY. *Bulletin of the Johns Hopkins Hospital* [*Bull. Johns Hopk. Hosp.*] **94**, 289–318, June, 1954. 6 figs., 41 refs.

The authors present, from Johns Hopkins University and Hospital, Baltimore, a detailed comparative clinical study of 15 cases of classic sickle-cell anaemia (S–S) with 16 cases of sickle-cell–haemoglobin C disease (S–C), 4 cases of sickle-cell–thalassaemia disease (S–thal.), and 3 of sickle-cell–congenital haemolytic jaundice (S–CHJ). The patients were classified according to the results of filter-paper electrophoresis of the haemoglobin, examination of other members of the family, and the results of haematological investigations.

All the cases of S–S and S–thal. manifested symptoms before the age of 10, whereas only 7 out of 16 in the S–C group did so. The S–S patients were asthenic and long-legged, while the others were more stockily built, and 14 of the 15 S–S patients, but only 3 from among the other groups, had tortuous retinal veins. All 15 patients in the S–S group had cardiomegaly and 12 of these had previously been considered to have rheumatic heart disease, while of the other groups only 3 had cardiac enlargement with essential hypertension. Presumably as a result of infarctions the spleen was never found enlarged after the age of 10 in patients with sickle-cell anaemia, but 9 out of the 16 in the S–C group had splenomegaly, including two patients aged 65 and 75. Haematuria occurred in a few cases in all three groups, but no cases of the nephritis peculiar to this disease were observed. Attacks of joint and bone pain were commoner in the S–S group than in the S–C group, but 5 of the 16 patients in the latter group developed osteochondritis of either the femoral or humeral head. Abdominal crises occurred in 14 out of 15 of the S–S group, but in only 2 cases of the S–C group and in none of the S–thal. group. Haemolytic crises occurred during pregnancy more often in the S–C group than in the S–S. In no patient of the S–S group was the haematocrit reading ever above 30%, but this figure was exceeded in every case in the other two groups. These findings are tabulated and discussed, together with 19 other cases of sickle-cell variants described in the literature.

The authors distinguish cases of sickle-cell anaemia which are homozygous from those which are heterozygous for the sickle trait, and which are, in addition, heterozygous for another erythrocyte abnormality. Some of the latter cases they think may have been regarded previously as of atypical sickle-cell anaemia.

[The 15 cases of classic sickle-cell anaemia studied were selected from a large number in the hospital records on the basis of completeness of data. The group appears to be very homogeneous, and its lack of diversity may over-emphasize the clinical contrast with the variant groups.] *A. J. Duggan*

432. **Adrenocortical Function and Metabolism of 17-Hydroxycorticosteroids in Pernicious Anemia**
A. A. SANDBERG, K. EIK-NES, D. H. NELSON, J. G. PALMER, G. E. CARTWRIGHT, and M. M. WINTROBE. *New England Journal of Medicine* [*New Engl. J. Med.*] **251**, 169–174, July 29, 1954. 7 figs., 8 refs.

The authors have conducted experiments at the University of Utah College of Medicine, Salt Lake City, to examine the claim of Strauss and Brokaw (*New Engl. J. Med.*, 1951, **245**, 798) that there is "functional adrenocortical insufficiency" in certain cases of pernicious anaemia in relapse.

Estimation of the plasma 17-hydroxycorticosteroid level in 8 cases of pernicious anaemia revealed normal values in all but one patient who was critically ill. After the oral administration of adrenal steroids (ACTH or hydrocortisone) there was a more rapid and sustained rise in the plasma level of 17-hydroxycorticosteroids than normal, but after intravenous injection the "clearance" of these steroids was unimpaired. The plasma level of 17-hydroxycorticosteroids rose normally in patients with pernicious anaemia after giving ACTH. In one patient with gastric achylia but without pernicious anaemia the level of 17-hydroxycorticosteroids was similar to that found in the plasma in cases of pernicious anaemia after the administration of adrenal corticoids by mouth. In patients with pernicious anaemia the administration of gastric juice along with adrenal steroids produced levels nearer to the normal.

The authors therefore conclude that there is no evidence of adrenal insufficiency accompanying pernicious anaemia, but that the changes they observed following the oral administration of adrenal corticoids to achylic patients were probably due to the absence of gastric juice, since normally a large fraction of the dose of corticosteroids is destroyed in the gastrointestinal tract before absorption can take place. *Nigel Compston*

433. **Absorption of Radioactive Vitamin B_{12} after Total Gastrectomy. Relation to Macrocytic Anemia and to the Site of Origin of Castle's Intrinsic Factor**
J. A. HALSTED, M. GASSTER, and E. J. DRENICK. *New England Journal of Medicine* [*New Engl. J. Med.*] **251**, 161–168, July 29, 1954. 1 fig., 21 refs.

The fact that a pernicious-like anaemia does not commonly follow total gastrectomy has led some workers to doubt whether the stomach is in fact the sole source of Castle's intrinsic factor. From the University of California Medical Center, Los Angeles, the authors report studies carried out on 11 patients who had undergone total gastrectomy, 11 normal subjects, 7 patients with pernicious anaemia, and 3 with idiopathic achlorhydria, the results of which have a bearing on this problem. The technique employed was that of Heinle

et al. (*Trans. Ass. Amer. Phys.*, 1952, **65**, 214) in which the percentage of an oral dose of vitamin B_{12} (cyanocobalamin) recovered in the faeces is used as an indication of absorption, the vitamin being labelled with radioactive cobalt (^{60}Co).

In the normal control subjects an average of 33% of the dose was recovered; in the patients with pernicious anaemia the amount recovered amounted to 97%, in the 3 cases of idiopathic achlorhydria to 34%, and in the 11 gastrectomized patients to 87%. In the last-named group and in those with pernicious anaemia the percentage excretion was reduced to 20 and 38 respectively following the administration of a source of intrinsic factor. The evidence therefore suggests that removal of the stomach in man removes the whole source of intrinsic factor.

The authors then discuss the reason why macrocytic anaemia is in fact unusual after total gastrectomy. They suggest that the liver stores of cyanocobalamin suffice to supply the patient for the limited survival time to be expected after the operation of total gastrectomy (which is usually performed for the treatment of carcinoma) since this period seldom exceeds 3 years. In some cases also a small portion of the fundus may be left after gastrectomy which is just enough to provide sufficient intrinsic factor; in others prophylactic treatment by the private physician may prevent the development of macrocytic anaemia—in 9 of the authors' 11 cases inquiry revealed that treatment had been given outside the hospital which was such as to prevent the appearance of macrocytic anaemia. Although none of these patients actually developed macrocytic anaemia, 10 had lost weight, 10 showed some degree of steatorrhoea, and 7 had developed an iron-deficiency anaemia.

Nigel Compston

HAEMORRHAGIC DISEASES

434. **Compounds E and F, and ACTH in the Management of Idiopathic Thrombocytopenic Purpura**

C. J. D. ZARAFONETIS, W. A. STEIGER, and S. K. CARY. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **228**, 1–15, July, 1954 9 figs., 11 refs.

The results of treatment with Compound E (17-hydroxy-11-dehydrocorticosterone) and Compound F (17-hydroxycorticosterone) and ACTH in idiopathic thrombocytopenic purpura are reported in this paper from the Temple University School of Medicine, Philadelphia. All cases in which an allergic or drug reaction appeared to be aetiologically significant were excluded. The L.E.-cell test was performed in all the 11 cases studied to exclude a diagnosis of systemic lupus erythematosus. The reaction to the Coombs test was positive in 3 cases, and in 2 there were positive reactions to repeated serological tests for syphilis. These last reactions were proved to be false by the treponemal immobilization test, and the authors emphasize the value of this test in excluding spirochaetal infection.

As a result of treatment haemorrhage was arrested in all cases; this was associated with an increase in capillary resistance. However, there was not always a comparable remission in the thrombocytopenia. In 3 cases in which the rise in the platelet count was negligible splenectomy was performed, with apparent cure in one, a partial improvement in one, and temporary improvement only in one. In a further case an increase in the platelet count was observed at first, but this was not maintained even during treatment. In the remaining 7 cases there was adequate haematological remission. The authors consider that 2 of these 7 patients were cured after one course of steroid; the condition of 2 others was satisfactory at the time of the report. In 3 cases the platelet count increased with each course of treatment but gradually fell thereafter.

There did not appear to be any difference in the response to oral administration of Compound E or Compound F, or to ACTH, but in one case Compound F given parenterally was ineffective although there was a response when the drug was later given by mouth.

Nigel Compston

435. **Prothrombin and Haemorrhage**

A. C. DONALD, R. B. HUNTER, G. R. TUDHOPE, W. WALKER, and I. WHITTON. *British Medical Journal* [*Brit. med. J.*] **2**, 961–963, Oct. 23, 1954. 1 fig., 12 refs.

In this paper from the University of St. Andrews Medical School, Dundee, the authors describe 4 cases in which haemorrhage occurred while the patients were receiving coumarin anticoagulants. Laboratory tests showed that the haemorrhagic state was associated with a very low true prothrombin activity rather than with very low levels of Factor VII.

The authors also describe 2 cases of hepatic disease in which subcutaneous haemorrhage was a prominent feature. In both cases there was a true hypoprothrombinaemia of severe degree, but the clotting time as determined by the one-stage Quick test was only moderately prolonged, owing to mild deficiency of Factor VII.

A. Brown

436. **Concentrated Human Antihaemophilic Globulin.** [In English]

P. G. HOORWEG, G. J. H. DEN OTTOLANDER, and M. A. E. DEKKER. *Vox Sanguinis* [*Vox Sang. (Amst.)*] **4**, 92–97, Sept., 1954. 1 fig., 9 refs.

A solution of the fibrinogen–antihaemophilic-globulin fraction obtained from human plasma by Cohn's method of fractionation distillation and containing 200 mg. of fibrinogen in 10 ml. was found to have 3 times the antihaemophilic activity of fresh citrated plasma. However, only if 60 to 80 ml. was administered to a haemophiliac was the concentration of antihaemophilic globulin in the plasma still increased after 24 hours. To obtain a higher concentration of the globulin the fibrinogen was first removed by heating at 56° C. for 5 minutes, causing coagulation. Then, by dialysis against saline with 1% glucose, an isotonic preparation was obtained which possessed an activity twenty times that of fresh citrated plasma. After sterilization by filtration this preparation can be stored in lyophilized form. *A. Brown*

Respiratory System

437. **The Management of Serous Primary Pleural Effusion in Young Adults**
J. MACKAY-DICK and N. G. ROTHNIE. *Tubercle* [*Tubercle* (*Lond.*)] **35**, 182–187, Aug., 1954. 2 refs.

The treatment given at the Connaught Hospital, Hindhead, to 50 young adults with pleural effusion consisted in repeated aspiration of the chest until no more fluid could be obtained, breathing exercises, and administration of streptomycin intramuscularly and isoniazid by mouth, this treatment extending over a period of 6 months; this was followed by rest in bed for 3 months and convalescence for 6 months. The results of this treatment were compared with those obtained in 140 similar cases treated by rest only. In 33 of the patients in the latter group the fluid extended above the level of the second rib, and in 18 of these the fluid resolved within a year; however, in all of 10 patients with effusions of similar size who were treated by the more active method the fluid disappeared within 9 months. In 55 of the conservatively treated group the fluid extended to between the second and fourth ribs, and in 31 it resolved within 6 months and in 52 within a year. Of 32 patients with similar effusions treated by aspiration the fluid disappeared within 6 months in 24 and within a year in the remainder. *J. R. Bignall*

LUNGS AND BRONCHI

438. **Lipoid Granuloma of the Lung**
R. A. DANIEL and T. M. NOLEN. *American Surgeon* [*Amer. Surg.*] **20**, 849–862, Aug., 1954. 8 figs., 13 refs.

In this paper from the Vanderbilt School of Medicine, Nashville, Tennessee, the pathology and symptoms of lipoid granuloma of the lung are discussed and 7 cases are described in detail. A history of repeated ingestion of mineral oil usually taken at bedtime, for constipation, was obtained in all cases, and in 2 oily nasal drops had also been used. It is pointed out that when the oil reaches the alveoli it is emulsified and most of it is phagocytosed by large macrophages (foam cells). An inflammatory exudate occurs in the alveoli, the oil becomes enveloped in fibrous tissue, and later the alveoli are progressively obliterated. The oil also reaches the hilar lymph nodes and these are gradually replaced by fibrous tissue. The lesions may be firm, diffuse, or nodular, and can vary in size from a few millimetres to the diffuse involvement of an entire lung. Macroscopically, the condition presents an appearance closely resembling that of carcinoma.

The presenting symptom in the present series was a chronic cough with or without sputum, haemoptysis, repeated respiratory infection, dyspnoea, or wheezing. The radiological appearances, which varied considerably, did not conform to any pattern, and were indistinguishable from those of carcinoma. The upper lobe only was involved in 4 cases, and both upper and lower lobes were involved in 2. In all the cases the condition was unilateral. Oily droplets were found in the sputum in only one of the 5 cases in which the sputum was examined. There were no clear-cut features in the symptomatology, or in the results of ancillary investigations, which permitted differentiation of lipoid granuloma from carcinoma, and in 5 of the 7 cases pneumonectomy was erroneously performed. The authors express the hope that by placing greater emphasis on a history of the ingestion of oil and on examination of the sputum for oil droplets an accurate diagnosis may be reached in these cases [although the absence from the sputum of oil droplets does not exclude a lipoid granuloma]. *R. L. Hurt*

439. **Carcinoma of the Bronchus with Bence Jones Proteinuria**
J. T. HUGHES. *British Medical Journal* [*Brit. med. J.*] **2**, 1267–1268, Nov. 27, 1954. 12 refs.

440. **Long-term Oxytetracycline (Terramycin) Therapy in Advanced Chronic Respiratory Infections**
W. H. HELM, J. R. MAY, and J. L. LIVINGSTONE. *Lancet* [*Lancet*] **2**, 630–633, Sept. 25, 1954. 15 refs.

The authors, working at the Brompton Hospital, London, studied the effect of long-term administration of oxytetracycline in cases of advanced chronic respiratory infection. The initial dosage was usually 2 g. daily and the maintenance dose 1 to 1·5 g. daily. In all cases sputum was cultured after preliminary homogenization of the sputum specimen with pancreatin.

Considerable success was achieved in the case of a 4-year-old girl suffering from fibrocystic disease of the pancreas associated with gross pulmonary changes; over a period of 2½ years this patient remained in reasonable health while taking 0·25 g. of oxytetracycline every 6 hours, but experienced a relapse each time the drug was stopped. Of 17 cases of chronic bronchitis, 15 responded well to long-term therapy, the drug being taken for 7 to 28 months in 9 cases. One patient with severe persistent bronchitis did well on a maintenance dose of 2 g. a day, but each time this was reduced to 1 g. the sputum and cough increased. In 13 cases of infective asthma the clinical response was poor because of the increase in viscosity of the sputum during treatment. Of 7 patients with bronchiectasis 6 responded well immediately to treatment, with reduction in cough and sputum, 4 of them maintaining this improvement during continued administration of the drug for periods of 6 to 8 months. *Haemophilus influenzae* was isolated from the sputum in 25 of the 37 cases. Toxic effects of oxytetracycline were limited to mild abdominal disturbances. Vitamin-B complex was given to most of the patients, including all those treated for long periods.

The authors consider that the results achieved in this series are sufficiently definite to justify continuation of the treatment and the setting up of a controlled investigation. *E. G. Rees*

441. **Pulmonary Postural Drainage for Bronchiectasis**
J. G. Russo. *Diseases of the Chest* [*Dis. Chest*] **26**, 81–91, July, 1954. 5 figs., 18 refs.

The author points out the difficulties encountered by some bronchiectatic patients, particularly the elderly, in adopting the positions which are usually prescribed for postural drainage, and goes on to describe 4 methods which he has elaborated from personal experience.

(1) In the first, the knee–chest position, the patient is supported on the knees and forearms with the thighs perpendicular to the floor and the pelvis well above shoulder-level. Expulsive coughing in this position is alternated with a period of rest sitting back on the heels with the body erect. (2) From Position 1 each lung base may be drained in turn by resting on the knees and one forearm with the trunk rotated so that the lung being drained is uppermost. The author believes that the frequency and amount of time spent in postural drainage are best judged by the patient himself. (3) The elbow-to-knee position. In this the patient sits, legs apart, on the edge of a chair with the body flexed as far down as possible and the elbows below knee level. Or without the chair he may bend well down with knees slightly flexed and elbows resting on knees. Each lung may be drained by appropriate rotation of the trunk. The importance of periods of rest is emphasized. (4) In the fourth position, which is recommended especially for the arthritic, the patient crouches almost as though about to start a sprint and, leaning well forward, supports himself with one forearm on one chair and the other hand on a second chair so that one shoulder is higher than the other. The importance of explanation to the patient in order to secure his cooperation is emphasized.

[Personal trial by the abstracter has shown that some of the positions are not as simple as might be supposed from the illustrations which accompany the article. All the methods seem to drain mainly the lower lobes and the efficacy of some of them is open to doubt.]

L. Capper

442. **Ligation of the Pulmonary Arteries or Their Branches in Difficult Cases of Pulmonary Resection.** (A propos de la ligature des artères pulmonaires ou de leurs branches dans les exérèses difficiles)
P. Hertzog and L. Toty. *Poumon* [*Poumon*] **10**, 395–408, May, 1954.

According to the authors, the greatest operative hazard of pulmonary resection is damage to major vessels which it is intended to preserve. They advise that in any difficult case a clamp or temporary ligature be applied to the appropriate pulmonary artery, if necessary within the pericardium, to provide a clearer field of operation. They describe in detail the approach and the difficulties likely to be encountered during the removal of right and left lungs as well as individual lobes. They claim that with such a ligature and digital pressure any bleeding can be controlled, most vascular injuries can be repaired, and much unnecessary sacrifice of healthy lung tissue may be avoided.

J. Robertson Sinton

443. **Cystic Pulmonary Sequestration with Abnormal Arterial Supply.** (La séquestration pulmonaire kystique avec artère anormale d'origine aortique)
M. Jaubert de Beaujeu, A. Marmet, J. Touzard, and H. Boucher. *Poumon* [*Poumon*] **10**, 409–420, May, 1954. 10 figs., 4 refs.

A description is given of 6 new cases of localized cystic disease of the lower lobes of the lungs associated with an abnormal artery to the cystic area. In each case air- and fluid-containing cavities were noted in the posterior parts of one or other lower lobe. At operation the lobe involved was found to contain large cysts, often secondarily infected, though communication with a bronchus was only once demonstrated. The hazard of operation was greatly increased by the presence of a large artery (ranging in size up to that of the femoral artery) arising directly from the descending aorta, crossing the triangular ligament, and entering the cystic area. In one case a corresponding vein entered the inferior vena cava. These cases were similar to those described by Pryce *et al.* (*Brit. J. Surg.*, 1947, **35**, 18; *Abstracts of World Surgery*, 1948, **3**, 121).

[This paper is one of 7 presented at a meeting of the Société de Chirurgie Thoracique de Langue Française reporting a total of 14 cases of this condition.]

J. Robertson Sinton

444. **The Change in the Arterial Oxygen and Carbon Dioxide Tension during Voluntary Hyperventilation as a Test of Lung Function**
V. O. Björk and H. J. Hilty. *Journal of Thoracic Surgery* [*J. thorac. Surg.*] **27**, 541–545, June, 1954. 1 fig., 8 refs.

In 21 healthy individuals studied at Sabbatsberg Hospital, Stockholm, it was found that during maximal hyperventilation arterial blood samples showed an average increase in oxygen tension of 23 mm. Hg and an average decrease in carbon dioxide tension of 19 mm. Hg. In 35 patients with unilateral tuberculosis the average changes were 8·4 and 4·3 mm. Hg respectively, while in 31 patients with bilateral tuberculosis and in 11 patients with far advanced tuberculosis the changes were insignificant, except for an increase of 6 mm. Hg in arterial carbon dioxide tension in the "poor-risk" patients, possibly owing to the large amount of work being done by their respiratory muscles during hyperventilation.

Of the 11 poor-risk patients with advanced disease, one died after operation, 7 remained respiratory cripples, and 3 were able to return to work. [The authors give no detailed information on the postoperative course of the other patients.] It is argued that inability to raise arterial oxygen tension and lower arterial carbon dioxide tension during hyperventilation indicates a very poor respiratory reserve. [Since the poor-risk patients had a very low maximum breathing capacity, it is possible that this measurement alone might have been an equally good test—but details are not given.] *W. A. Briscoe*

Otorhinolaryngology

445. **Atrophic Rhinitis**
R. L. RUGGLES. *Archives of Otolaryngology* [*Arch. Otolaryng.* (*Chicago*)] **59**, 747–748, June, 1954. 4 refs.

Six cases of atrophic rhinitis are described, in some of which the author noted an increased number of eosinophil leucocytes in the nasal secretions. It is known that in the treatment of allergic rhinitis by Hansel's method a slight overdose of dust extract temporarily increases nasal congestion. With this in mind the author gave increasing doses of dust and mould extract in these cases in the hope of producing turbinal oedema. Eventually the turbinals did in fact become oedematous and crusting ceased. The dose causing the desired effect was maintained and the interval between injections gradually lengthened. He found that there were two types of case —those where the disease was reversible and continuous treatment was not needed, and those in which the patient did well while under treatment, but relapsed as soon as it was stopped. *F. W. Watkyn-Thomas*

446. **Modern Aspects of the Recruitment Phenomenon**
M. P. LANSBERG. *Archives of Otolaryngology* [*Arch. Otolaryng.* (*Chicago*)] **59**, 712–730, June, 1954. 4 figs., 44 refs.

The author discusses a number of fallacies which have arisen in regard to the effect of the recruitment phenomenon on hearing. It appeared at first sight that in cases of recruitment deafness (that is, deafness of cochlear type) hearing would be nearly normal when threshold loss was compensated for by use of a hearing aid, since the loudness of speech is above the threshold level. It was found, however, that the intelligibility of speech is seriously affected by the sound distortion present in this kind of deafness. This distortion is caused by (*a*) dynamic dysacousis—" an accelerated loudness sensation versus sound pressure function "; (*b*) diplacusis, with discrepancy in pitch impression between the two ears; (*c*) disharmonic paracusis, which alters the character of sounds perceived; and (*d*) " self masking " or auditory fatigue. The author accepts Hallpike's suggestion that recruitment is associated with cochlear lesions but not with neural lesions, and points out that the absence of recruitment noted several years previously by de Bruïne-Altes in cases of presbyacusis implied that there were fundamental differences in cases of perceptive deafness of different origin. He admits that there are difficulties in the interpretation of certain findings on this basis—for instance, in herpes oticus, where the lesion is regarded as a ganglionitis, he has found recruitment to be present, and suggests that here there may be a hydrops of the scala media producing a Ménière-like condition of the labyrinth; similarly in disseminated sclerosis he has not been able to prove the absence of recruitment, though this is still under investigation. He concludes that " differential diagnosis in cases of perceptive deafness can usually be based on the presence or absence of recruitment. The functional testing, however, becomes difficult in many cases of partial recruitment in which complex situations exist ".

The study of recruitment has elucidated some of the effects on hearing of trauma, fatigue, and adaptation, and has given further evidence of how the middle-ear muscles can change the impedance of the sound-conduction apparatus. " The change varies for the different frequencies and for bone and air conduction and depends on the status in the cavum tympani." It is emphasized, however, that since " normal loudness relations are finally represented by two dimensions, space and time ", and " pathological processes in hearing usually involve more than one station in the long road from drum membrane to cortex ", it is futile to attempt to explain phenomena of hearing on an oversimplified basis.
F. W. Watkyn-Thomas

447. **Circulation of the Spiral Ligament and Stria Vascularis of Living Guinea Pig**
F. L. WEILLE, S. R. GARGANO, R. PFISTER, D. MARTINEZ, and J. W. IRWIN. *Archives of Otolaryngology* [*Arch. Otolaryng.* (*Chicago*)] **59**, 731–738, June, 1954. 8 figs., 14 refs.

In operations carried out on more than 500 guinea-pigs under anaesthesia the cochlea was fenestrated and the spiral ligament observed with a microscope at ×200 magnification. A special table was used to eliminate all vibration, and oxygen delivered through a tracheotomy to abolish respiratory movement. Vessels [described as arterioles] were seen to pass towards the base of the cochlea to supply (*a*) a capillary network in the spiral ligament, (*b*) branches deep among the pigment cells to feed the capillaries of the stria vascularis, and (*c*) a few branches passing directly over the stria to empty into venules. These last are thought to be identical with Agazzi's " arteriovenous arcades ". All the arterioles, arteriovenous arcades, and venules were seen to contract and dilate independently, the lumen disappearing and reappearing. Although similar changes were seen in single capillaries as well as whole networks, the independent contractility of the capillaries was not definitely determined, since such changes might be due either to active contraction or to passive collapse caused by the shutting off of the arteriolar blood supply.
F. W. Watkyn-Thomas

448. **Fenestration and Experimental Nystagmus. Studies by Rotation, Caloric Stimulation and Fistula Tests.** [In English]
K. E. PURSIAINEN. *Acta oto-laryngologica* [*Acta oto-laryng.* (*Stockh.*)] Suppl. 112, 1–97, 1954. Bibliography.

Urogenital System

449. **Proteinuria Variations in the Differentiation of Renal Disorders. Clinical Implications**
S. E. KING. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **155**, 1023–1026, July 17, 1954. 13 refs.

Routine tests carried out during medical examination of young adults before enlistment revealed an unexpectedly high proportion with proteinuria; the reagent used for the detection of albumin in the urine was 20% sulphosalicylic acid solution. In order to distinguish those patients with proteinuria due to renal disease from those with proteinuria due to posture or to transient causes all positive reactors were admitted to the U.S. Army Hospital, Fort Jay, New York, for a 3-day observation period, during which a dry diet, low in sodium chloride and protein, was given, the patients being allowed moderate activity. Urine passed in the recumbent or standing position at specified intervals was examined, and it was found that in 542 (16%) of 3,309 cases the proteinuria was due to previously asymptomatic chronic glomerulonephritis or pyelonephritis. Irregular proteinuria, the cause of which could not be ascertained with certainty, was present in 204 (6·1%) of the patients during the first period of observation in hospital; when readmission permitted further investigation it was found in some cases that an abnormality within the urogenital system, but not an abnormality of the nephron, was the cause. Orthostatic proteinuria was not always a continuous feature. The author believes that emotional stress is a factor in the irregular recurrent type of proteinuria. He points out that while in some cases proteinuria is undoubtedly sporadic and clinically insignificant, this does not justify the conclusion that it will eventually subside. *L. H. Worth*

450. **The Fanconi Syndrome and Its Clinical Variants**
R. M. MYERSON and B. H. PASTOR. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **228**, 378–387, Oct., 1954. 3 figs., bibliography.

451. **The Hormone Treatment of Lipoid Nephrosis.** (Le traitement hormonal de la néphrose lipoïdique)
R. DEBRÉ, P. MOZZICONACCI, and C. ATTAL. *Annales de médecine* [*Ann. Méd.*] **55**, 238–251, 1954. 3 figs., 27 refs.

At the Hôpital des Enfants Malades, Paris, 44 children suffering from lipoid nephrosis but without any detectable signs of nephritis were selected for treatment with ACTH or cortisone, or both. Each course lasted 7 to 10 days, the dosage of ACTH being 75 to 150 mg. daily in four doses by intramuscular injection, and of cortisone 150 to 200 mg. daily in two separate injections, or by mouth two 25-mg. tablets every 6 hours. In 18 cases one course of treatment only was given, the remainder having between 2 (9 cases) and 14 courses (2 cases). A salt-free, high-protein diet was regarded as a useful adjuvant; salt was added according to the loss in the urine.

Of the 44 patients, 10 recovered and remained free from recurrences for periods exceeding one year, and 3 remained in good health for 6 to 12 months. In 11 cases a "partial" success was achieved, consisting in temporary improvement with increased diuresis and loss of oedema, whereas in 3 further cases, although there was some improvement, normal blood electrolyte levels were not regained. Another group of 3 patients deteriorated during observation and developed signs of subacute renal failure. There were 7 deaths, one of which occurred within 24 hours of the beginning of a second course of ACTH. The remaining 7 patients could not be traced. The authors are of the opinion that hormone treatment is of value in speeding up recovery and shortening the duration of an acute attack but does little to improve the over-all recovery rate, bearing in mind the fact that remissions are known to occur with other therapeutic measures. *L. H. Worth*

452. **Acute Tubular Necrosis with Anaemia**
J. WAGNER. *Great Ormond Street Journal* [*Gt Ormond Str. J.*] 7, 66–72, June, 1954. 1 fig., 14 refs.

453. **The Results of Chemotherapy in Urinary Infections**
L. P. GARROD, R. A. SHOOTER, and M. P. CURWEN. *British Medical Journal* [*Brit. med. J.*] **2**, 1003–1008, Oct. 30, 1954. 4 refs.

The value of chemotherapy in urinary-tract infections is discussed in the light of results obtained in 686 cases seen at St. Bartholomew's Hospital, London, between September, 1952, and August, 1953. Of the 1,022 infections in these 686 patients, 726 were treated with sulphonamides and 5 different antibiotics, the highest immediate over-all cure rate being obtained with "sulphatriad", sulphadimidine, and penicillin. The sensitivity of the causative organism was determined before and immediately after treatment, a clear relationship being established between the sensitivity *in vitro* and the outcome of treatment. Specimens of urine were obtained after treatment from 562 patients, and of these 378 were free from infection; a follow-up examination of 317 specimens from 512 treated patients revealed that 205 specimens were still free from infection.

Assessment of cure in terms of urinary sterility showed that the best results were obtained in patients without urinary-tract abnormality and without a previous history of urinary infection, 16 out of 20 men and 157 out of 178 women being cured. Of 34 men and 159 women with a history of urinary infection, 16 of the former and 118 of the latter were cured, but of 116 men and 55 women with urinary-tract abnormality, only 39 and 32 respectively were cured. The prognosis depended to a signi-

ficant degree on the species of the infecting organism; coccal infections, especially those due to *Streptococcus faecalis*, responded best, with coliform infections next; other organisms, especially *Pseudomonas aeruginosa* and paracolon bacilli, were much more difficult to eliminate.

There was little to choose between the different drugs used in this investigation, but the results suggest that the sulphonamides have a place in the treatment of urinary-tract infections. The authors advocate the use of laboratory sensitivity tests " to avoid the prescription of inappropriate drugs ". Moreover, if the development of chronic renal infection with its attendant dangers is to be prevented cure must be confirmed by microscopical examination of the urine immediately after treatment and again some months later. *Adrian V. Adams*

454. **Combined Electrolyte Therapy in Advanced Renal Disease Manifested by Azotemia and Acidosis**
R. A. NEUBAUER. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **227**, 628–639, June, 1954. Bibliography.

The author records, from the Memorial Hospital, Wilmington, Delaware, a trial of intensive alkali therapy on 20 patients critically ill with terminal renal disease. They included 11 cases of chronic glomerulonephritis, 4 of chronic pyelonephritis, 2 of polycystic kidney disease, and 3 of hydronephrosis with postobstructive uraemia and acidosis. In all cases any infection, dehydration, or obstruction had been corrected, and a low-protein, high-calorie diet administered, but no improvement had been obtained.

Baseline studies were first made on non-comatose patients while they received 1 g. of salt, 20 to 40 g. of protein, a high-calorie diet, and 2,500 to 3,000 ml. of fluid per day; during the trial they also received 40 ml. of molar sodium lactate solution (a precursor of bicarbonate) 4 or 5 times daily, 20 to 40 ml. of 10% calcium lactate in aluminium hydroxide gel 4 times a day as a precaution against tetany, and in some cases also 5 to 10 ml. of molar potassium acetate 3 or 4 times daily, all given by mouth. Comatose patients received all therapy intravenously until they were well enough for oral feeding. At 10 a.m. they were given 1,000 to 1,500 ml. of 5% glucose in water containing 2 to 6 g. of calcium gluconate and 10 units of soluble insulin, with 2 to 4 g. of potassium as the chloride or acetate if the serum potassium level was normal or below normal and the circulation and urine volume were satisfactory. At 4 p.m. they received 120 to 240 ml. of molar sodium lactate with 0·5 g. aminophylline, and an equal volume of 5% glucose in water if oedema and cardiac impairment were not present. At 10 p.m. the morning infusion was repeated. Anaemia had to be treated in some cases. Fluid intake and urinary output were carefully measured, the urine analysed for sodium, potassium, and chloride content, and the blood urea nitrogen and serum sodium, potassium, and chloride levels and CO_2-combining power determined.

Most patients required this regimen even after discharge, but all except one were partially or completely rehabilitated. The blood urea nitrogen value fell in all cases and the alkali reserve rose, probably owing to the formation of bicarbonate from lactate. The serum chloride level also fell and there was an initial sodium retention. Side-effects due to the treatment were few. Of the 20 patients, many of whom were *in extremis* when the treatment was begun, 7 are still alive after 20 to 27 months, and most of the 13 who have died had many months of reasonably good health.

It is emphasized that the regimen is still in the investigative stage and requires strict supervision and proper facilities for biochemical control. *Thomas B. Begg*

455. **Physiological Mechanisms Regulating Rate of Urinary Flow in Renal Disease**
A. G. WHITE and G. RUBIN. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol. (N.Y.)*] **86**, 30–36, May, 1954. 8 figs., 12 refs.

The excessive excretion of water which occurs in chronic renal disease may be due to one of two mechanisms, namely, osmotic diuresis or tubular secretion of water. In an attempt to determine which of these mechanisms is responsible the authors studied, at Mount Sinai Hospital, New York, the urinary excretion of water and solutes in 4 healthy young males (who served as controls) and in 7 patients, of whom 4 had chronic glomerulonephritis, one chronic pyelonephritis, one polycystic kidneys with severe renal insufficiency, and one acute glomerulonephritis. All were given fluids *ad lib.* and the diet of those with renal disease contained only 200 mg. of sodium per day.

It was found that whereas the normal subjects excreted 0·4 to 1·5% of their glomerular filtrate as urine, in those with renal disease this figure ranged from 1·9 to 36%. In the latter the urine was hypotonic to plasma in 5 cases, and hypotonic in regard to sodium and chloride in all 7 patients. It was observed that the proportions of glomerular filtrate excreted as urine were paralleled more closely by the clearance ratio of the total solutes than by that of sodium, potassium, chloride, or urea, suggesting that the total solutes rather than any single one determine the amount of excretion of water. As, moreover, there was a linear relationship between the urinary osmotic load and the rate of urinary flow, it is concluded that osmotic diuresis is the major physiological mechanism regulating rate of urinary flow in renal disease.

From this study it appears that in chronic renal disease the critical glomerular filtration rate is about 10 ml. per minute, and that below this level the clearance rate for potassium exceeds the glomerular filtration rate, the proportion of filtered water excreted exceeds 15% (the accepted maximum in health), and the relationship of this percentage to the urinary concentration of sodium, potassium, and total solutes is altered. Full details of the authors' procedure and methods of calculation are given. *Thomas B. Begg*

456. **Uremic Pericarditis in Acute and Chronic Renal Failure**
W. WACKER and J. P. MERRILL. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **156**, 764–765, Oct. 23, 1954. 6 refs.

Endocrinology

PITUITARY GLAND

457. **Corticotropic Activity of Human Blood**
J. PARIS, M. UPSON, R. G. SPRAGUE, R. M. SALASSA, and A. ALBERT. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **14**, 597–607, June, 1954. 28 refs.

The authors present a concise review of the present position in regard to assays for corticotrophin in human blood, and discuss the merits and demerits of various techniques that have been developed, particularly in the Mayo Foundation laboratories, Rochester, Minnesota, since the earlier report by Taylor *et al.* (*Endocrinology*, 1949, **45**, 335; *Abstracts of World Medicine*, 1950, **7**, 294).

They consider that the method of Sayers *et al.* (*Endocrinology*, 1948, **42**, 379), which depends on the measurement of adrenal ascorbic-acid depletion in hypophysectomized rats, is still on the whole the most reliable, though in their experience it has some limitations: for example, the assay rat must be completely hypophysectomized, and the method cannot be depended on for quantitative measurement of ACTH activity, the results obtained having tended to be capricious. Another reliable method, although it requires comparatively large amounts of blood, is that employed by Sydnor and Sayers (*Proc. Soc. exp. Biol. (N.Y.)*, 1952, **79**, 432), who used extracts of blood prepared by the oxycellulose process of Astwood and his colleagues. By both these methods corticotrophic activity has been demonstrated in Addison's disease, the adrenogenital syndrome, and in a few miscellaneous conditions, whereas no activity could be detected in normal persons or in patients with Cushing's disease or febrile miliary tuberculosis. A number of other workers have claimed to have found high corticotrophic activity in normal serum, but their results have so far been too contradictory to be relied on.

Richard de Alarcón

458. **The Starvation State and Functional Hypopituitarism**
W. H. PERLOFF, E. M. LASCHÉ, J. H. NODINE, N. G. SCHNEEBERG, and C. B. VIEILLARD. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **155**, 1307–1313, Aug. 7, 1954. 2 figs., 17 refs.

Severe nutritional deficiency often leads to functional impairment of the endocrine system, and in extreme degrees of malnutrition the clinical picture may easily be confused with that associated with destruction of the anterior lobe of the pituitary gland (Simmonds's disease). In order to assess their value in differential diagnosis, various laboratory tests of endocrine function have been carried out by the authors of the present paper at the Philadelphia General Hospital (Temple University School of Medicine) on 5 subjects suffering from gross undernutrition (due to anorexia nervosa in 4 cases and to non-tropical sprue in one) and the results compared with those obtained from normal controls and in 9 cases of proved hypopituitarism.

Thyroid function was investigated by estimation of the 24-hour uptake of radioactive iodine and of the ability of the gland to respond to pituitary thyrotrophic hormone; the basal metabolic rate and serum cholesterol level were also measured. Evidence of marked hypothyroidism, apparently due to reduced pituitary stimulation, was found in the starvation state, but in contrast to true hypopituitarism this was shown to be reversible if refeeding could be achieved. Moreover, a low serum cholesterol level was found to be common in starvation, but not in pituitary disease. Gonadal function was assessed by means of urinary oestrogen, 17-ketosteroid, and gonadotrophin determinations. Diminution of function comparable in degree to that occurring in hypopituitarism was found in all cases of inanition, being in fact the earliest endocrine manifestation, but again activity could be restored by refeeding. Adrenocortical function was measured by a variety of tests, the findings in most of which showed some degree of hypoadrenocorticism associated with starvation, and in none provided a clear distinction between malnutrition and pituitary disease. The beneficial effects of refeeding were again apparent in the biochemical findings.

It is concluded that starvation may markedly affect the function of the pituitary gland, but that no laboratory test can differentiate between hypopituitarism due to this and that due to other causes. Functional hypopituitarism, however, differs from organic hypopituitarism in that it may be reversed by refeeding and that it does not respond adequately to specific endocrine therapy.

Nancy Gough

459. **Antidiuretic Activity of Human Urine after Surgical Operations**
V. D. EISEN and A. A. G. LEWIS. *Lancet* [*Lancet*] **2**, 361–364, Aug. 21, 1954. 3 figs., 9 refs.

In experiments carried out at the Middlesex Hospital, London, and the Buckston Browne Research Farm antidiuretic activity was observed in alcohol-anaesthetized rats which had received an intravenous injection of human urine passed during the first 24 hours after a surgical operation. When such urine was similarly injected into dogs in which the neurohypophyseal tracts had been sectioned, antidiuretic activity was again demonstrated. In the rat the dose–response curve for urine was similar to that for a solution of vasopressin. When the urine was made alkaline with sodium hydroxide and boiled its antidiuretic activity was destroyed. The addition of sodium thioglycolate to the urine or to the vasopressin solution also destroyed the antidiuretic activity. Urine obtained from healthy subjects who had inhaled tobacco smoke to the point of nausea, and from

subjects who had received an intravenous injection of vasopressin, when tested in the same way also showed antidiuretic activity. For these and other reasons the authors consider that the antidiuretic activity found in the urine after operation is due to the presence of an antidiuretic hormone. *G. A. Smart*

THYROID GLAND

460. **Treatment of Subacute Thyroiditis with Cortisone**
R. C. HUNTER and D. J. SHEEHAN. *New England Journal of Medicine* [*New Engl. J. Med.*] **251**, 174–177, July 29, 1954. 1 fig., 21 refs.

In this short communication from the Tripler Army Hospital, San Francisco, 3 cases of subacute thyroiditis in which treatment with cortisone in doses decreasing from 300 mg. daily proved valuable are briefly described and 15 other cases from the literature reviewed. In each case there was a prompt response to treatment, both the general and local condition improving within 24 hours of starting therapy. Relapse occurred if treatment was stopped too soon. The mechanism of action of cortisone in these cases is not clear; the authors suggest that the effect is primarily suppressive, but suffices to control the symptoms while the disease runs its usual self-limiting course. *Nigel Compston*

461. **The Clinical Importance of Angioreceptors of the Thyroid Gland.** (Клиническое значение ангнорецепторов щитовиъной железьі)
V. I. AKIMOV. *Клиническая Меыицина* [*Klin. Med. (Mosk.)*] **32**, 49–52, Sept., 1954. 3 figs.

It has been observed that during operations on the thyroid gland for goitre cardiovascular disturbances are liable to arise at the moment of ligating or dividing the thyroid arteries, being manifested most commonly by restlessness, facial hyperaemia, tachycardia, and changes in blood pressure. These phenomena occur even if there is minimal tension or trauma to the gland itself, and must be regarded as reflex responses to stimulation of the vascular receptors. The superior thyroid artery arises from the external carotid in close relation to the carotid sinus and carotid body, the inferior thyroid artery from the subclavian close to the sensitive receptor zone of the aortic arch.

In a study of these reactions the author has prepared stained sections of the perivascular tissue and adventitia of the superior thyroid arteries. These have revealed a network of fine nerve fibres, some of which terminate in button-like endings similar to a Vater–Paccini corpuscle, the remainder of the fibres spreading into the adventitia and becoming lost in it. Other nerve-endings, the shape of a small bean, consist of a retort-like sheath, to which three nerve-fibres run; of these, two which are unmyelinated enter the sheath, while the third (doubtfully myelinated) surrounds it and loses itself in the vascular adventitia. Similar though less numerous structures were observed on the inferior thyroid arteries. In one preparation two bean-like bodies were seen to be confined in one capsule; the flattened surfaces of these were opposed to each other and separated by a narrow chink filled with a transparent lymphoid fluid which bathed the whole intracapsular surface of the two corpuscles. To the external (convex) surface of each corpuscle ran a non-myelinated nerve fibre which penetrated its structure, while the outer capsule was covered with a neurovascular network. The shape of these intracapsular disks varied with the slightest alteration of position of the capsule, as did the distribution of the intracapsular fluid.

In the author's opinion this evidence points to the fact that the highly sensitive reflex area centred in the carotid sinus extends to the thyroid arteries and regulates not only the blood supply of the thyroid gland but also its secretory activity. Since it has been established by Chernagorsky, Merkulov, and Anichkov that there are links between the carotid sinus and the cerebral cortex, it would seem likely that similar links exist between the thyroid gland and the cortical and subcortical nuclei, particularly in view of the known influence of emotional disturbances on the development of thyrotoxicosis.

The author describes a case of severe thyrotoxicosis in which bilateral subtotal thyroidectomy was considered too great a risk, but in which procaine blockade produced a great decrease in tachycardia and in the size of the gland which lasted for 48 hours, although after this time the patient's condition returned to its previous state. Larish reported a case of a large parenchymatous goitre which, after the performance of periarterial sympathectomy of the right superior thyroid and part of the external carotid arteries, shrank and eventually disappeared on the right side, diminishing in size also on the opposite side after about a month. The author praises the technique of Nikolaev, who refuses to ligate the main thyroid arteries, and ties only the terminal branches as they pass through the fourth fascia (and of course the vessels in the gland itself). The author's own method is to perform subcapsular resection of the gland without ligating the thyroid arteries on their course to the thyroid; he has not observed any severe postoperative thyrotoxic crises since employing this technique. *L. Firman-Edwards*

462. **Coexistent Myxoedema Heart Disease and Psychosis**
R. J. CALVERT, E. SMITH, and L. G. ANDREWS. *British Medical Journal* [*Brit. med. J.*] **2**, 891–894, Oct. 16, 1954. 2 figs., 32 refs.

The authors report, from Whipps Cross Hospital, London, 2 cases of myxoedema associated with heart disease and accompanied by acute psychotic episodes. The first patient was a woman aged 48 who had classic symptoms of myxoedema, an enormous heart, but normal blood pressure. She was given ½ grain (32 mg.) of thyroid extract daily and after 3 weeks' treatment developed acute mania. The dosage was increased rapidly to 8 grains (0·52 g.) daily without signs of cardiovascular distress and she became rational again after 6 days. The daily dose of thyroid extract was later reduced to 6 grains (0·4 g.) and finally to 4 grains (0·26 g.). At

follow-up examination the cardiac condition was found to be nearly normal The second patient was a woman aged 58 who was admitted with mania. She had classic symptoms of myxoedema and congestive heart failure, and was given thyroid, ½ grain (32 mg.) daily, increasing gradually to 3 grains (0·2 g.) daily. After 3 weeks the cardiac failure had disappeared and her mental state had improved greatly.

These cases illustrate the dramatic effect of thyroid therapy on both the heart disease and the psychosis associated with myxoedema. The risk of producing acute congestive heart failure by giving large doses of thyroid extract is considered in relation to the need for these large doses to relieve the mental disorder.

A. C. Crooke

463. **Clinical Value of the Plasma Butanol-extractable (Thyroxine) I^{131} in the Diagnosis of Hyperthyroidism and Myxedema**

A. L. SCHULTZ, S. SANDHAUS, H. L. DEMOREST, and L. ZIEVE. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **14**, 1062–1068, Sept., 1954. 2 figs., 14 refs.

The plasma levels of butanol-extractable radioactive iodine (^{131}I) (B.E.I.) and of protein-bound ^{131}I (P.B.I.) were estimated and their relative values in assessing thyroid function were studied at the Veterans Administration Hospital and University of Minnesota, Minneapolis. Samples of plasma were taken from 50 euthyroid, 12 hyperthyroid, and 5 myxoedematous patients 24 hours after they had received 150 μc. of ^{131}I by mouth, a well-type scintillation counter being used for measuring the thyroid uptake and plasma level.

The levels of both B.E.I. and P.B.I. revealed a clear distinction without overlap between the euthyroid patients and those with clinically marked hyperthyroidism, but the values in myxoedematous subjects showed scatter through the normal range. The ratio between the two levels was similar in all three groups and was of no diagnostic value. In contrast, the ratio of plasma B.E.I. content to total plasma ^{131}I content in the euthyroid group was distinctly different from that in the hyperthyroid group, while this ratio was generally low in established myxoedema, although the values overlapped the normal range.

In euthyroid subjects the plasma levels of both B.E.I. and of P.B.I. varied over a narrower range than either the iodine uptake or the basal metabolic rate.

C. L. Cope

464. **Comparative Distribution and Fate of I^{131}-Labeled Thyroxine and Triiodothyronine**

P. VANARSDEL, J. R. HOGNESS, R. H. WILLIAMS, and N. ELGEE. *Endocrinology* [*Endocrinology*] **55**, 332–343, Sept., 1954. 8 figs., 25 refs.

Comparisons were made, at various time intervals, of the distribution in rat tissues of L-thyroxine and 1-3,5,3′ triiodothyronine, labelled with equal amounts of I^{131} with similar specific activity. At each interval studied, the concentration of triiodothyronine in plasma was much lower than that of thyroxine and somewhat lower in liver, except for an unexplained, but significantly higher, concentration 5 minutes following administration. Triiodothyronine was present in higher concentrations in kidney during the first 12 hours after administration; its concentration then dropped to below that of thyroxine. In skeletal muscle, concentrations of both hormones were relatively low, but the level of triiodothyronine was significantly higher than that of thyroxine during the first twelve hours. These concentrations rose gradually to a peak at six hours and then fell slowly. Relatively large amounts of iodide were observed to be present.—[Authors' summary.]

465. **Oxygen Consumption of Erythrocytes from Patients with Various Thyroid Conditions Related to Their Respective Serum Protein-bound Iodine Concentrations**

L. ANGELONE, D. H. WATKINS, and C. A. ANGERER. *Blood* [*Blood*] **9**, 953–958, Oct., 1954. 1 fig., 27 refs.

ADRENAL GLANDS

466. **The Effect of Insulin on the Levels of Adrenaline and Noradrenaline in Human Blood**

H. WEIL-MALHERBE and A. D. BONE. *Journal of Endocrinology* [*J. Endocr.*] **11**, 285–297, 1954. 8 figs., 32 refs.

The effect of insulin on the concentration of adrenaline and noradrenaline in human plasma was studied in patients undergoing insulin shock therapy at Runwell Hospital, Wickford, Essex. Fasting patients were given an intramuscular injection of 50 to 300 i.u. of insulin, which was just sufficient to elicit hypoglycaemic coma 3 to 4 hours later. After the patients had been in coma for periods up to one hour glucose was administered. Some patients received an intravenous injection of 0·1 unit of insulin per kg. body weight in the fasting state. Blood samples were collected at given times by puncture of an antecubital vein or the brachial artery. The blood was drawn directly into a solution of sodium fluoride and sodium thiosulphate, and the levels of adrenaline and noradrenaline were estimated by the differential fluorimetric method. If a large proportion of the catechol amines in plasma was associated with the blood platelets, these could be determined by this method.

After intramuscular injection of insulin there was an immediate fall in the adrenaline concentration in plasma; termination of coma was followed by a return of the adrenaline concentration to the initial level (about 1·6 μg. per litre). The concentration of noradrenaline did not alter significantly. Similarly, intravenous injection of insulin resulted in a fall in the adrenaline level, which reached its lowest point in about 5 minutes, but again the noradrenaline level did not change significantly. Larger doses of insulin by intravenous injection simply delayed the spontaneous return of the plasma adrenaline level to normal. The termination of hypoglycaemic coma by intravenous administration of glucose was accompanied by a rapid rise in the plasma adrenaline level, but there was no appreciable change in the plasma concentration of noradrenaline.

Intravenous injection of insulin in a dosage of 0·1 unit per kg. body weight caused a fall in the adrenaline concentration in venous blood which preceded a similar effect in the arterial blood. The authors consider that there was a transitory increase in the arterio-venous difference in concentration of adrenaline.

[Limitations of the method may be important in arriving at these conclusions. It should be noted, however, that the changes in the concentration of adrenaline usually preceded those in the blood sugar level.]

G. B. West

467. **The Effect of Glucose and Fructose Ingestion on the Adrenaline and Noradrenaline Levels in Human Plasma**
H. WEIL-MALHERBE and A. D. BONE. *Journal of Endocrinology* [*J. Endocr.*] **11**, 298–303, 1954. 3 figs., 22 refs.

Having observed that administration of glucose during hypoglycaemic coma results in a rise in the plasma level of adrenaline [see Abstract 466], the authors carried out further experiments to determine whether this effect of glucose was confined to the hypoglycaemic state and whether it was shared by other monosaccharides.

It was found that a dose of 50 g. of glucose given by mouth to fasting subjects produced a steep rise in the plasma concentration of adrenaline, which reached a maximum after 10 minutes. The level of noradrenaline did not change. The rise in the blood sugar concentration was much slower than that of adrenaline. There was no significant change in the blood level of either catechol amine in response to a dose of 50 g. of fructose. Thus the effect of glucose indicates a highly specific mechanism which causes either an increased discharge or a decreased utilization of adrenaline.

In some cases insulin in a dosage of 0·1 unit per kg. body weight was given by intravenous injection 15 minutes after 50 g. of glucose had been taken. The mean blood sugar level fell to 60% of the normal during the first 60 minutes while there was a transitory but definate fall in the plasma level of catechol amines. [In producing this rather confused picture, it may be that several factors, including pituitary stimulation, play a part.]

G. B. West

468. **Effect of Adrenocorticotropic Hormone and Cortisone Acetate on the Urinary and Blood Levels of Ascorbic Acid in Man**
J. C. BECK, J. S. L. BROWNE, and K. R. MACKENZIE. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **14**, 1006–1022, Sept., 1954. 10 figs., 21 refs.

At McGill University Clinic, Royal Victoria Hospital, Montreal, the authors have studied the effect of ACTH and cortisone acetate on the blood and urinary ascorbic acid levels of 32 chronically diseased patients receiving supplements of 250 or 1,000 mg. of the vitamin, or on a normal diet containing from 15 to 90 mg. of ascorbic acid per day.

Of 27 patients receiving ACTH, 21 showed an increased urinary excretion of ascorbic acid extending over the first 24 to 48 hours of hormone administration, and a reduction of excretion on withdrawal of the hormone. Of 9 patients receiving cortisone acetate intramuscularly, 3 showed similar changes in ascorbic acid excretion; in 6 cases there was no response, possibly owing to slow absorption of the cortisone, since 3 patients receiving cortisone by mouth all showed increased excretion of ascorbic acid. The dietary level of ascorbic acid did not appear to affect the type of response observed. Two scorbutic infants also showed a rise in urinary ascorbic acid excretion after injection of ACTH, together with an increase in the urinary content of formaldehydogenic corticoids and coincident clinical improvement.

In general the blood levels of ascorbic acid rose along with the urinary levels. The possible sources of the increased ascorbic acid output and the endocrinological implications of the results are discussed. It is suggested that increased glomerular filtration rate, lowered tubular reabsorptive capacity, and release of ascorbic acid from the adrenal cortex may all play a part.

F. W. Chattaway

469. **Effect of ACTH on the Adrenals in the Nephrotic Syndrome and Rheumatic Fever**
B. H. LANDING and D. FERIOZI. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **14**, 1023–1028, Sept., 1954. 2 refs.

In a study carried out at the Children's Medical Center (Harvard Medical School), Boston, the adrenal glands of 3 untreated patients with the nephrotic syndrome due to chronic glomerulonephritis were smaller in weight and had a higher fat content than the glands from patients with untreated rheumatic fever. Administration of ACTH (corticotrophin) to the nephrotic patients produced an increase in zone thickness and cell size in all 3 zones of the adrenal cortex, these values returning to normal on withdrawal of the hormone. In the patients with rheumatic fever ACTH provoked a greater response in the zona fasciculata than in the zona reticularis.

F. W. Chattaway

470. **The Effects of Aldosterone in Addison's Disease and Adrenal Pseudohermaphroditism**
F. T. G. PRUNTY, R. R. MCSWINEY, I. H. MILLS, and M. A. SMITH. *Lancet* [*Lancet*] **2**, 620–624, Sept. 25, 1954. 5 figs., 15 refs.

The authors have studied the effect of aldosterone on the metabolism of electrolytes, water, and corticosteroids in 2 patients treated at St. Thomas's Hospital, London. In the first case, that of a patient who suffered from Addison's disease and had been receiving deoxycortone acetate, the replacement of this treatment by the intramuscular injection of 200 μg. of aldosterone in oil was followed by a profound fall in urinary sodium output in the subsequent 24 hours and a 5-fold rise in the ratio of potassium to sodium in the urine. Further injections were followed by a retention of sodium exceeding in amount that of chloride, and by some degree of water retention, while the injection of a large dose (400 μg.) of aldosterone produced a transfer of water from the intracellular to the extracellular compartment, accompanied by a fall in the haematocrit reading. Aldosterone did not, however, restore water diuresis to normal. Plasma sodium and chloride levels fell, the blood pressure was

not unduly raised, and the number of eosinophil leucocytes was unaffected, but there appeared to be a significant rise in the blood sugar level.

In the other case, that of a girl of 13 with congenital adrenal pseudohermaphroditism, intramuscular injection of aldosterone (100 to 350 μg. daily) caused a slight rise in plasma sodium and chloride content. The excretion of 17-ketosteroids, however, remained at the former high level while aldosterone was given, although it fell rapidly in response to cortisone. *B. Nordin*

PANCREAS

471. **Metabolic Effects of the Pancreatic Hyperglycemic Factor**

N. KALANT. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol. (N.Y.)*] **86**, 617–619, July, 1954. 14 refs.

The author describes experiments carried out at McGill University Clinic, Montreal, to determine the effect of the " pancreatic hyperglycaemic factor " (HGF) on rats fasted for 24 hours; blood samples for analysis were taken from the jugular vein. The first group of rats were given an intraperitoneal injection of 33 μg. of HGF in dilute sodium hydroxide, two more such injections being given at intervals of one hour. Four hours after the initial injection a second sample of blood was taken and all blood specimens were analysed for total ketone content by the method of Lester and Greenberg (*J. biol. Chem.*, 1948, **174**, 903). A second group of rats received injections of 50 μg. of HGF at 6, 10, 14, and 22 hours after the start of fasting, blood being withdrawn after 24 hours of fasting. A third group of animals were treated in the same way as Group 2, but in this case the total dose of HGF was 600 μg. per day; blood was then taken for determination of sugar content, and samples of liver for glycogen content. Control animals in these 3 groups received only injections of the sodium hydroxide used as a solvent. A fourth group were given first NaOH only, and one week later the same plus 600 μg. of HGF, the urine being analysed for total nitrogen content on both occasions, so that each rat acted as its own control.

HGF caused a fall in the degree of the ketonaemia which had developed as a result of the fast, but did not affect the blood sugar level. When given during the fast HGF greatly inhibited the development of ketonaemia, increased the nitrogen excretion, and inhibited to some degree the rise in liver fat content; it did not affect the liver glycogen content or the blood sugar level.

I. McLean Baird

472. **Paradoxical Hyperglycemia in Diabetic Patients Treated with Insulin**

G. T. PERKOFF and F. H. TYLER. *Metabolism* [*Metabolism*] 3, 110–117, March, 1954. 5 figs., 16 refs.

Some diabetic patients show marked variation in the degree of hyperglycaemia and glycosuria present in spite of constant diet and insulin dosage. In such patients episodes of hypoglycaemia may be followed by periods of increased glycosuria, and efforts to abolish the glycosuria by increasing the dose of insulin may lead to a state of alternating glycosuria and aglycosuria which is difficult to control. The authors have observed 10 patients whose diabetes became more difficult to control as the insulin dosage was increased, whereas reduction of the dose of insulin resulted in a decrease of hyperglycaemia and glycosuria. Seven of the patients were middle-aged or elderly, and reduction of their insulin dosage to approximately half its former amount was associated with rapid amelioration of hyperglycaemia and glycosuria. For example, a man aged 71 was taking 110 units of insulin daily and yet was excreting 25 g. of glucose daily; 48 hours after reduction of the dose of insulin to 60 units his daily glucose excretion had fallen to 2·5 g. and remained at this level for many months. The other 3 patients were young diabetics whose insulin dosage could not be reduced so abruptly. Gradual reduction by 2 or 3 units at a time, however, abolished wide fluctuations in the degree of glycosuria present, and the daily output of glucose was ultimately less than it had been with the higher dose of insulin.

The findings in these cases show that excessive insulin dosage may aggravate hyperglycaemia and glycosuria in some diabetic patients. This paradox may be explained as being due to an exaggerated hyperglycaemic response to the hypoglycaemia caused by excessive insulin. Attempts to demonstrate the occurrence of subclinical hypoglycaemia in these patients gave inconclusive results, although in some cases administration of large doses of insulin resulted in a marked fall in the blood sugar level immediately after a meal in contrast to the usual postprandial hyperglycaemia. Paradoxical hyperglycaemia occurred both with short-acting and with long-acting insulins. *K. O. Black*

473. **Insulin Resistance as a Sequel of Insulin Overdosage and its Treatment with Thiouracil Compounds.** (Insulin-resistenz als Folge von Insulin Überdosierung und ihre Behandlung mit Thiourazilverbindungen)

C. BRENTANO. *Zeitschrift für klinische Medizin* [*Z. klin. Med.*] **152**, 371–390, 1954. 3 figs., 44 refs.

Writing from the Ospedale Maggiore, Milan, the author, after pointing out that the insulin requirement for the control of diabetes is seldom a constant quantity, proceeds to advance evidence based on clinical observations on diabetic patients and on experimental findings in rabbits to show that chronic overdosage with insulin can give rise to a higher or lower degree of insulin resistance. He suggests that this is due to thyroid hyperfunction, although possibly adrenal and other mechanisms may be involved. The insulin resistance may be removed by treatment with phenylthiouracil. A number of illustrative case histories are presented.

[The original article should be consulted for details of the lengthy discussion.] *Norval Taylor*

474. **Chemical, Biological, and Physiological Background of the New Insulin-zinc Suspensions**

K. HALLAS-MØLLER. *Lancet* [*Lancet*] **2**, 1029–1034, Nov. 20, 1954. 18 figs., 12 refs.

The Rheumatic Diseases

475. **Complementary Activity of the Blood in Rheumatism and Certain Allied Disorders**
C. E. KELLETT. *Annals of the Rheumatic Diseases* [*Ann. rheum. Dis.*] **13**, 211–218, Sept., 1954. 12 figs., 8 refs.

The author, working at the General Hospital, Newcastle upon Tyne, estimated the complementary activity in the blood of patients with rheumatic fever, rheumatoid arthritis, lupus erythematosus, and spondylitis, and in a group of non-rheumatic patients who acted as controls, by adding varying dilutions of patients' sera to sensitized sheep erythrocytes, the resulting haemolysis being assessed colorimetrically.

In the control group the levels of complementary activity were within a narrow range, but in 79 cases of rheumatoid arthritis the range was greater, although in most instances still within normal limits; in one of these cases, however, in which psoriasis was associated, the activity was very low. There was a marked diminution of complementary activity in 2 cases of disseminated lupus erythematosus, and in one case of ankylosing spondylitis. In the 2 cases of rheumatic fever there were insignificant changes during the active phase of the disease, but the complementary activity rose to high levels during convalescence. In discussing these results the author recalls that agglutination tests are usually positive in rheumatoid arthritis and negative in ankylosing spondylitis, psoriasis arthropathica, and disseminated lupus erythematosus, and it was in the cases of these last three conditions that the complementary activity was found to be lowest. The author explains this " on the assumption that both agglutinins and complement had become used up by some form of reaction ".

F. Clifford Rose

476. **A Skin Test with Streptolysin O.** (Test cutaneo alla O-streptolisina)
G. CORBELLI and M. A. BRUNELLI. *Minerva medica* [*Minerva med. (Torino)*] **2**, 871–875, Oct. 10, 1954. 5 figs., 17 refs.

At the University Medical Clinic, Bologna, skin tests were performed with a commercial product, used for the estimation of serum antistreptolysin, which contains a known amount of streptolysin O and small amounts of other streptococcal products. In this method the amount of streptolysin is expressed in terms of a " combining unit ", which is defined as the maximim quantity of toxin which, in the presence of a unit of antistreptolysin, does not produce haemolysis of 0·5 ml. of rabbit erythrocytes in 5% isotonic solution. A quantity ranging from 0·1 to 0·15 ml. of a solution of this lyophilized, standardized, and sterilized streptolysin containing one combining unit in 1,000 or 2,000 ml. was injected into the flexor surface of the forearm. [No control injections were apparently given, except as stated below.] The reaction was regarded as positive when there was a fairly intense, clearly demarcated oedema and erythema, reaching its maximum after 20 to 30 hours and then gradually but completely disappearing. Results were read at 24 hours; reactions less than 10 mm. in diameter were ignored, and larger positive reactions were graded according to degree. The test was performed on 152 " normal " subjects (that is, persons considered free from streptococcal infection), 136 patients with upper respiratory infections, and 108 with rheumatic disease. In addition, 94 " normal " subjects were similarly tested with a suspension of a 24-hour culture containing 5,000,000 haemolytic streptococci per ml.

In the normal subjects the proportion of positive reactions to streptolysin O averaged 9·8%, and to the streptococcal suspension 30·8%. In patients with acute infections of the upper respiratory tract positive reactions to streptolysin occurred in 52·9%, and in those with chronic infections in 92·1%. No constant correlation with organisms found in the throat was established, and no definitive explanation of the findings is offered. Of 23 patients with articular rheumatism also tested, 22 gave positive results, while of 85 patients with rheumatic cardiac lesions but no articular lesions, a positive result was obtained in 56 cases. The occurrence of positive reactions coincided with clinical and pathological indications of activity. The authors suggest that cardiac lesions become evident only when activity is diminishing and when positive reactions to this test are accordingly less frequent.

W. A. Bourne

477. **Comparative Effects of Aspirin, ACTH, and Cortisone on the Antistreptolysin " O " Titer and Gamma Globulin Concentration in Rheumatic Fever**
B. L. STOLZER, H. B. HOUSER, and E. J. CLARK. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **44**, 229–234, Aug., 1954. 2 figs., 9 refs.

The comparative effects of aspirin, ACTH, and cortisone on the serum antistreptolysin-O titre and γ-globulin concentration in rheumatic fever was studied at a U.S. Air Force Base Hospital in Wyoming. A total of 144 young adult males was divided by random selection into 3 groups, receiving respectively aspirin, ACTH, and cortisone. The drugs were given in a diminishing dosage for 6 weeks in all except 8 cases, these requiring a further 4 weeks' treatment because of continued rheumatic activity. An intramuscular injection of 600,000 units of penicillin was given on the day of admission and then every 3 days for 4 injections; thereafter each patient received 1 g. of sulphadiazine by mouth daily.

The antistreptolysin-O titre and the γ-globulin concentration were estimated weekly in half the patients and at 10-day intervals in the remainder. The average values week by week for each of the 3 treatment groups are plotted on graphs. These show that both values fell most rapidly in the group receiving ACTH and least

rapidly in the group receiving aspirin. It is stated [though the evidence is not given] that at the end of treatment the values were significantly lower in the ACTH group than in either of the other two groups, and that the difference between the values in the cortisone-treated group and those in the group receiving aspirin was not statistically significant. After treatment ceased there was a slight increase in the average γ-globulin concentration in all 3 groups, coincident with a slight " rebound ", which was noted clinically in some cases. Thereafter there was a continued fall, and 14 months after the start of treatment the average γ-globulin concentration was the same in both the ACTH- and cortisone-treated groups, the concentration in the aspirin-treated group being slightly higher.

The authors suggest that the difference between the effect of ACTH and that of cortisone may have been related to the dosage of each drug, the patients receiving cortisone showing fewer signs of hyperadrenalism.

B. E. W. Mace

478. **Results of Hormone Therapy in Acute Rheumatic Carditis.** (Résultats du traitement hormonal de la maladie de Bouillaud)

P. MOZZICONACCI, J. NOUAILLE, C. ATTAL, and M. K. CARAMANIAN. *Bulletins et mémoires de la Société médicale des hôpitaux de Paris* [*Bull. Soc. méd. Hôp. Paris*] **70**, 786–795, July 2, 1954.

The authors give an interim report on the treatment with steroid hormones of 267 cases of rheumatic fever associated with carditis, some of which have been observed for more than 2 years. The results have varied; in most cases, however, the treatment was rapidly successful in reducing the activity of recurrent attacks, and this has led them to adopt steroid therapy as the basal treatment for this disease. They consider that it should be employed early in all cases of acute rheumatism, whether accompanied by carditis or not. They also give salicylates, and regard the use of antibiotics in addition as helpful in certain types of case preventing the occurrence of bacterial endocarditis on the site of an old valvular lesion.

W. S. C. Copeman

479. **Quinacrine (Atabrine) in Treatment of Systemic and Discoid Lupus Erythematosus**

E. L. DUBOIS. *Archives of Internal Medicine* [*Arch. intern. Med.*] **94**, 131–141, July, 1954. 19 refs.

480. **Alimentary Tract in Disseminated Scleroderma with Emphasis on Small Bowel**

H. L. ABRAMS, W. H. CARNES, and J. EATON. *Archives of Internal Medicine* [*Arch. intern. Med.*] **94**, 61–81, July, 1954. 6 figs., 36 refs.

After a brief review of the literature the authors, from Stanford University School of Medicine, San Francisco, report 6 cases of scleroderma in which, in addition to the well-recognized oesophageal lesions, there were widespread lesions of the intestinal tract. These involved the duodenum, jejunum, and ileum, and their presence was suggested clinically by anorexia, abdominal pain, and loss of weight. Radiological examination revealed alteration in the calibre (dilatation), tone, peristalsis, and motility of the affected bowel. The cases are illustrated by excellent reproductions of radiographs and of photomicrographs of post-mortem material.

In 3 of the 6 cases the course was rapidly progressive, death occurring within 2 years of the onset of symptoms. The characteristic finding at necropsy in these cases was loss of muscle fibres in the muscularis without appreciable replacement by fibrous tissue.

Treatment with cortisone or corticotrophin produced a temporary remission in 2 other cases, and in the remaining case resection of the oesophagus and gastroenterostomy were performed for the relief of dysphagia.

Nigel Compston

CHRONIC RHEUMATISM

481. **The Ocular Manifestation of Ankylosing Spondylitis.** (Les manifestations oculaires de la spondylarthrite ankylosante)

P. MICHAUD and J. FORESTIER. *Revue du rhumatisme et des maladies ostéo-articulaires* [*Rev. Rhum.*] **21**, 489–496, June, 1954. 19 refs.

The ocular manifestations of ankylosing spondylitis are in general confined to the uvea. The reported incidence of uveitis has varied widely. In the authors' series of 200 cases of ankylosing spondylitis uveitis was seen in 17 cases (8·5%); in this group no other eye affection, such as the Gougerot–Sjögren syndrome, was observed. They point to the great rarity of uveitis in rheumatoid arthritis, and are convinced that uveitis and spondylitis are manifestations of a common morbid process.

The symptomatology of uveitis is discussed. Attacks may be repeated at intervals for some years before the appearance of the first somatic symptoms of spondylitis, and they often occur in the early pre-ankylosing phase of the disease. It is particularly important, therefore, when confronted with a case of uveitis in a young man, even if it is accompanied only by vague " rheumatic " pains, to remember this possibility and investigate the radiological appearances of the sacro-iliac joints. The clinical forms of uveitis, which vary in severity and gravity, are fully described. The benign form is liable to be mistaken for conjunctivitis; it manifests itself by slight symptoms and signs of iritis, very slight pain, some photophobia and lacrymation, and a sluggish pupil reaction, but usually abates spontaneously in 8 to 10 days. In more marked attacks there is some pericorneal injection, and some fragile synechiae may form. More severe is the typical form, an acute diffuse uveitis of sudden onset. Here there is marked photophobia with the usual signs of inflammation of the iris, but only a slight tendency to the formation of posterior synechiae. These attacks also generally subside fairly quickly, leaving no residual signs, but in rare cases may progress to a more severe form resulting in total uveitis, with severe pain, marked signs of iritis, and affection of the vitreous. During the following 6 to 8 weeks the condition slowly abates, although some posterior synechiae persist. Much more severe are the granulomatous forms

of uveitis; these follow recurrences of simple iritis, are characterized by a tendency to form tough posterior synechiae, and nodules may be observed in the iris. The most serious of all, however, is torpid uveitis, which begins quietly with mild symptoms and progresses steadily and insidiously over months or years, with the formation of very strong synechiae which, by occluding the pupil, may lead to total blindness.

The treatment is discussed. In the authors' practice atropine, to obtain and maintain pupillary dilatation, is always combined with repeated instillations of cortisone. If this fails, subconjunctival injections of cortisone and adrenaline are tried; in still more resistant cases hyaluronidase is given in addition. In severely painful attacks the authors advise the early retrobulbar injection of 1 to 2 ml. of 40% alcohol. *Kenneth Stone*

482. **Zone Electrophoretic Studies of Plasma Proteins in Rheumatoid Arthritis and Ankylosing Spondylitis**
T. E. HUNT and J. A. TREW. *Annals of the Rheumatic Diseases* [*Ann. rheum. Dis.*] **13**, 201–210, Sept., 1954. 10 figs., 7 refs.

The authors report, from the General Hospital, Regina, Saskatchewan, the results of the determination of plasma protein levels by zone electrophoresis in 20 cases of rheumatoid arthritis, 5 of ankylosing spondylitis, and in 18 normal subjects. Fibrinogen levels were also estimated, both by precipitation and electrophoresis, and related to the erythrocyte sedimentation rate. The average duration of the rheumatoid condition was 4½ years, most of the patients being in the advanced stage of the disease.

In the cases of ankylosing spondylitis and rheumatoid arthritis a rise in the plasma fibrinogen and γ-globulin content was found, the albumin fraction being correspondingly reduced, and there was a linear correlation between the erythrocyte sedimentation rate and the plasma fibrinogen level. The administration of cortisone reduced both these values, but when gold salts and phenylbutazone were given in addition there was no further alteration. No significant change in the levels of the α- and β-globulin fractions was observed. The detailed results are presented graphically and in tables.

[Most other workers have found some alteration in the α-globulin fraction. The electrophoretograms illustrated do not show a satisfactory separation of the various protein fractions, presumably because the amount of serum applied was too great in relation to the thin filter paper used.] *F. Clifford Rose*

483. **A Contribution to the Oral Gold Therapy of Rheumatism.** (Beitrag zur peroralen Goldtherapie des Rheumatismus)
B. SCHREINER and G. STEPANTSCHITZ. *Medizinische* [*Medizinische*] **33/34**, 1112–1114, Aug. 21, 1954. 6 refs.

The authors maintain that gold still plays a valuable role in the treatment of rheumatoid arthritis and that there is room for new preparations of low toxicity. They have recently observed at the University Medical Clinic, Graz, Austria, the effects of a complex preparation, "aurubin", containing gold salts among a number of other constituents, which can be taken by mouth in the treatment of various rheumatic conditions, mostly rheumatoid arthritis. In this disease its effects were less obvious in cases of recent onset than in more chronic cases; in 11 out of 35 of the latter with sufficient follow-up, improvement was noted within 4 to 7 days. Side-effects (mainly nausea and diarrhoea) were encountered in 8 cases, but there was no occurrence of leucopenia, albuminuria, or haematuria. Excretion of 17-keto-steroids was unaffected and no change was observed in the number of circulating eosinophil leucocytes. It is assumed that gold is the active principle in this complex preparation, but its mode of action has yet to be elucidated and further studies are in progress. *D. Preiskel*

484. **The Investigation of Synovial Exchange by Means of Radioactive Sodium (^{24}Na).** (Les échanges synoviaux. Leur mesure à l'aide du radio-sodium Na^{24})
F. COSTE, M. BOUREL, and F. MOREL. *Annales de médecine* [*Ann. Méd.*] **55**, 360–392, 1954. 12 figs., 31 refs.

Writing from the Rheumatological Clinic, Faculty of Medicine, Paris, the authors describe a method for the measurement of synovial exchange in which, after injecting radioactive sodium (^{24}Na) in an isotonic solution intra-articularly, they record its disappearance from the joint by means of a Geiger–Müller counter to which is attached a graphic recorder; this method has the advantage over those used previously in that the injection does not interfere with normal metabolism. It was found that in animals of the same species and age the graphs obtained obeyed constant laws.

Sodium permeability depends upon two factors—the state of the connective tissues and the blood supply—and one or other of these was varied in the study here reported of synovial exchange in the knee-joint of the rabbit. The connective-tissue barrier was altered by injections of testicular hyaluronidase and, as expected, the clearance of ^{24}Na was more rapid. The blood supply was altered either by femoral arteriectomy, when the clearance was less even after the injection of hyaluronidase, or by the injection of vasodilator substances; however, the results obtained were equivocal after administration of acetyl-β-methylcholine, and no alteration in synovial clearance was found when sodium nicotinate was given.

The synovial exchange was also measured after inflammation in the joint had been produced by repeated intra-articular injections of ethanolamine oleate, the effect of steroids on the exchange taking place in the inflamed joint being then ascertained. It was found that systemic administration of cortisone or intra-articular injection of deoxycortone acetate or hydrocortisone slowed down exchange when this was initially rapid, and increased it when it was initially slow. The authors stress that since the experimentally induced inflammatory reaction altered the basic structure of synovial connective tissue, the results obtained in this study are not necessarily applicable to inflamed joint conditions in the human patient.
F. Clifford Rose

Neurology and Neurosurgery

485. **Subacute Combined Degeneration of the Cord and Achlorhydric Peripheral Neuropathies without Anaemia**
E. C. O. JEWESBURY. *Lancet* [*Lancet*] **2**, 307–312, Aug. 14, 1954. 18 refs.

The author describes 5 cases of subacute combined degeneration of the cord with achlorhydria in which the bone marrow was normal and there were insignificant changes in the peripheral blood.

In 2 of the cases pernicious anaemia was not diagnosed and the patients were given aneurin and ascorbic acid, the second patient receiving a little vitamin B_{12} (cyanocobalamin) in addition. Both patients improved and were discharged; 2 years later the condition relapsed and the patients were readmitted, when the blood count and the bone-marrow picture were typical of pernicious anaemia and there were severe neurological symptoms, which in one case progressed to a fatal outcome in spite of intensive treatment with cyanocobalamin. In the other 3 cases cyanocobalamin was given, although the laboratory findings were negative; pernicious anaemia did not develop, the neurological signs were arrested, and there was symptomatic improvement.

Peripheral neuropathy and achlorhydria with a normal blood picture were observed in 2 further cases. Both patients were given cyanocobalamin with subjective improvement, but the neurological signs showed no change. The author discusses the difficulty in these cases of differentiating deficiency of cyanocobalamin from other nutritional deficiencies. In one of the cases of peripheral neuropathy and 2 of the cases of subacute combined degeneration of the cord giant metamyelocytes (giant stab cells) were seen in an otherwise normal marrow, indicating a maturation disturbance of the leucocyte series; the author considers that this finding is a valuable aid in establishing a diagnosis of deficiency of cyanocobalamin. He suggests that the comprehensive term "vitamin-B_{12} deficiency" should be used instead of the less precise and often inadequate terms "pernicious anaemia" and "subacute combined degeneration of the cord". *Richard de Alarcón*

486. **Electromyography in Intervertebral Disc Protrusions**
C. S. WISE and J. ARDIZZONE. *Archives of Physical Medicine and Rehabilitation* [*Arch. phys. Med.*] **35**, 442–446, July, 1954. 2 figs., 4 refs.

The authors, working at the George Washington University and Mount Alto Veterans Hospital, Washington D.C., set out to confirm the value of electromyography in determining the presence of nerve-root compression in 83 cases of the intervertebral disk syndrome. Of these cases (69 in men and 14 in women aged from 26 to 62), 6 were thought to be cervical nerve-root lesions and 77 lumbar root lesions. Electromyograms were recorded on a 6- or 8-channel Grass electroencephalograph, needle electrodes being inserted 2 to 4 cm. apart in the long axis of the muscles to be examined. Recordings were made after suitable relaxation periods, and the responses to cough, Valsalva's manœuvre, and volitional activity were observed; simultaneous bilateral records from the extremities were taken in all cases, and where possible the electromyogram was recorded before myelography was carried out. As the apparatus used had a frequency response limit of 70 c.p.s. the observations were therefore confined to normal or abnormal unit activity, and fibrillation potentials could not be recorded.

The finding of frequent spontaneous polyphasic discharges at rest in a localized segmental nerve-root distribution limited to one or two nerve-root segments was considered indicative of nerve-root compression. Bilateral spontaneous discharges were noted in many subjects showing a clinical picture of unilateral compression. The appearance of polyphasic spontaneous discharges following cough or the Valsalva manœuvre occurred in a small percentage [unstated] of cases, and when present was considered to be highly suggestive of nerve-root compression. Of the 83 cases, 41 were treated conservatively without myelography, and in these the electromyogram gave a positive result in 14 cases, was negative in 22 cases, and inconclusive in 5, the results being in general agreement with the clinical findings. Of the remaining 42 cases, both myelography and surgery were performed in 31 cases and myelography only in 11. Tables of the results comparing the findings by electromyography and myelography are given. The authors are of the opinion that preliminary electromyography may be of considerable value in deciding whether myelography is necessary. *Kenneth Tyler*

CEREBRAL VASCULAR DISORDERS

487. **Wallenberg's Syndrome. A Report of Twelve Cases with Special Reference to Prognosis.** [In English]
I. L. HULTÉN-GYLLENSTEN. *Acta psychiatrica et neurologica Scandinavica* [*Acta psychiat. neurol. scand.*] **29**, 79–87, 1954. 10 refs.

At Södersjukhuset, Stockholm, 12 cases of Wallenberg's syndrome (thrombosis of the posterior inferior cerebellar artery) were studied with particular reference to the rate of regression of the neurological signs and the resulting functional state in terms of working capacity. The interval between the follow-up examination, on which conclusions are based, and the initial thrombosis ranged from $1\frac{1}{2}$ months to 5 years.

The lesion was on the left side in 11 of the 12 cases. Two of the patients died within the first 14 days, death being due to the vascular lesion itself in one and to a coincident pulmonary embolism in the other. Horner's syndrome, which was present in all cases at the onset, regressed rapidly in the initial phase of recovery, but

persisted in 6 cases. Signs of cerebellar dysfunction similarly regressed in the first few months, persisting as a permanent disability in one patient only. Dysphagia, noted in the 10 survivors, disappeared within 7 days in 2 patients but persisted for one to 3 months in the remainder, although in no case did the symptom become a permanent disability.

Sensory abnormalities due to involvement of the nucleus of the trigeminal nerve occurred and persisted in 9 of the 10 survivors. Involvement of the spinothalamic tract was present in all cases at the onset; the sensory impairment disappeared within 6 weeks in one patient, remained unchanged in one, and persisted, though less marked in degree, in the remaining 8.

Of the 10 survivors, 3 died from heart disease within a year of the initial episode; 5 were able to resume normal working life after a period of one to 2 years; and 2 were unable to work, one because of associated cardiovascular disease and diabetes and the other because of ataxia in walking. *Fergus R. Ferguson*

488. **Peripheral Collateral Circulation between Cerebral Arteries. A Demonstration by Angiography of the Meningeal Arterial Anastomoses**

H. ROSEGAY and K. WELCH. *Journal of Neurosurgery* [*J. Neurosurg.*] **11**, 363–377, July, 1954. 6 figs., 34 refs.

The authors present, from the Letterman Army Hospital, San Francisco, the results of investigation by carotid angiography of the blood flow to the cerebral hemispheres in 3 patients, 2 of whom had suffered occlusion of the proximal part of a middle cerebral artery and one occlusion of both anterior cerebral arteries.

The first case was that of a child of 5½ years who had three attacks of transient left-sided weakness within one week and finally a complete flaccid hemiplegia. Angiography showed that the middle cerebral artery was blocked proximally by thrombosis, but all the distal branches showed excellent filling through the anterior cerebral and calloso-marginal arteries. Serial radiographs clearly showed the direction of the flow. Inhalations of carbon dioxide were given and a stellate ganglion block performed to produce vasodilatation in the cerebral vessels, but the improvement in the hemiplegia was slow and only partial recovery was obtained.

The second patient was a 30-year-old woman in whom the right middle cerebral artery had been clamped during an operation on an aneurysm. During the operation arterial hypotension had been induced by hexamethonium, and at that time there was paralysis of the left leg. When the blood pressure returned to its normal level movements of this limb were observed and recovery was rapid. On angiography the distal branches of the middle cerebral artery were seen to be filled by retrograde flow from the middle and posterior cerebral arteries.

The third patient was a woman aged 33 who had an aneurysm of the anterior communicating artery. The left anterior cerebral artery was occluded at operation, but previous angiography had shown that the right anterior cerebral artery was blocked. Right carotid angiography showed that distal branches of the anterior cerebral artery were filled by retrograde flow from the middle cerebral artery. This patient remained comatose and died some 4 months later. At necropsy both anterior cerebral arteries were found to be thrombosed and there was widespread softening of the frontal lobes.

Previous studies of the subject are fully discussed and emphasis is laid on the significance of blockage of the perforating arteries arising from the proximal part of the middle cerebral artery. Whereas the cortical branches have free anastomoses, the branches running to the internal capsule and the basal ganglia have not. In the authors' first case the anterolateral striate artery was probably blocked and so the hemiplegia persisted because of damage to the internal capsule; in the second case this did not occur. In any case the visual demonstration that the anastomotic channels are open does not necessarily indicate that flow is sufficient to prevent cerebral ischaemia.

[The term " meningeal arterial anastomoses " as used by the authors here seems misleading; surely a better term would be " cortical arterial anastomoses ". The present work may be compared with the experimental studies of the functional aspects of cerebral arterial anastomoses by McDonald and Potter (*J. Physiol.* (*Lond.*), 1951, **114**, 356).] *Donald McDonald*

489. **Chronic Cerebral Hypertensive Disease**

W. HUGHES, M. C. H. DODGSON, and D. C. MACLENNAN. *Lancet* [*Lancet*] **2**, 770–774, Oct. 16, 1954. 1 fig., 13 refs.

In this paper from Stapleton Hospital, Bristol, the authors discuss the personality changes and physical disabilities observed in 51 cases of chronic arterial hypertension, and the necropsy findings in 15 of them. In 3 cases, which are described in detail, a diastolic blood pressure above 120 mm. Hg was accompanied by the signs and symptoms usually associated with pseudobulbar palsy. In a further case the patient, a man of 74, had a diastolic pressure of 100 mm. Hg when admitted to hospital. Blood pressures were based on the highest recorded diastolic pressure [but since this was difficult to obtain accurately on some occasions and the circulation has to withstand the average diastolic pressure throughout the day and night this seems an unsound criterion for judging the clinical effect of hypertension. This patient would appear to have had senile dementia with arteriosclerosis rather than a condition resulting from hypertension].

There was no correlation between the severity of the symptoms and the height of the blood pressure; in some cases there was a fall in blood pressure after an acute " cerebral episode ". Among the symptoms and signs were emotional lability, pseudobulbar palsy, personality changes with evidence of intellectual deterioration, vertigo, and the various gradations of " stroke ".

The pathology in the cases coming to necropsy is discussed, especially the possible mechanism responsible for the multiple ischaemic patches seen in the basal ganglia. Often no actual occlusion of the vessels could be demonstrated and there were remarkably few lesions in the cortex of the brain. It is suggested that areas of the brain are deprived of their full blood supply by a reduction in flow from turbulence at the mouths of the

smaller vessels. [It is very doubtful if this is the correct explanation; most evidence points to spasm as the most likely cause of the ischaemia. This is a useful paper because the authors have collected under one heading several clinical states which have previously been described individually. The difficulty seems to be to know how far each is the result of hypertension, arteriosclerosis, or angiospasm, or a combination of these factors.]

G. S. Crockett

490. **Occlusion of the Carotid Arteries. Further Experiences**

M. FISHER. *Archives of Neurology and Psychiatry* [*Arch. Neurol. Psychiat.* (*Chicago*)] **72**, 187–204, Aug., 1954. 10 figs., 6 refs.

The author believes that carotid occlusion is a common condition and that routine examination of the cervical portion of the carotid arteries would reduce the still substantial incidence of unexplained cerebrovascular disease to less than 5%. In a series of 432 consecutive necropsies carried out at Montreal General Hospital, examination of the cervical portion of the carotid arteries showed that in 28 cases there was complete occlusion of one or both arteries and in a further 13 cases the arterial lumen was reduced to pinhole size, these 41 cases thus representing an incidence of advanced carotid disease of nearly 10%. This strikingly high incidence is more than three times that for thrombotic occlusion of the major vessels adjacent to the circle of Willis and is of the same order as that for cerebral haemorrhage and for hypertensive atherosclerotic encephalomalacia. In another series of admittedly selected patients at St. Anne's Veterans Hospital, Montreal, 17 cases of carotid occlusion were seen at necropsy in the course of 18 months; there were thus in all 45 cases of total occlusion.

From a study of these cases, some of which are described in detail, the author proposes a tentative classification based partly on the clinical and partly on the pathological findings, which are, however, complex. Fundamentally, carotid occlusion is a sequel of atherosclerosis. Plaques are especially liable to form within the carotid sinus at the origin of the internal carotid artery. Occlusion may arise from direct enlargement of the plaque itself, from superimposed thrombus formation, from haemorrhage into the plaque, from embolism, or probably most often from a combination of one or more of these events. Since atherosclerotic plaques in the carotid sinus are prone to ulcerate and so facilitate mural thrombus deposition, a cerebral embolus may easily take origin from this site; in this series, 4 cases were interpreted as being due to this cause. Bilateral carotid disease adds still further to the complexity of the pathological picture; among the author's cases, 10 fell into this category, 5 being associated with senile dementia and 5 with manifest bilateral neurological signs and coma. When occlusion is strictly unilateral, the condition may be either asymptomatic or symptoms of shock or anoxia may be precipitated. In 20 of the present cases sudden unilateral occlusion caused hemiplegia.

The carotid sinus was the most common site of atherosclerosis, but in 3 cases occlusion was caused by a large plaque blocking the left common carotid near its origin from the aorta, and in one by a plaque about 1 inch (2·5 cm.) proximal to the carotid sinus. The presence of coexisting but unrelated cerebrovascular disease may complicate the picture even further. The author found 7 cases of thrombo-embolic disturbances in other regions of the brain and 2 cases of unrelated hypertensive encephalomalacia. Most patients with carotid disease are over 55 years of age, but exceptions are not rare. In general, severely hypertensive patients tend not to have significant carotid disease. The author feels that it would be premature at this juncture to put forward concrete suggestions for the treatment of this condition and its protean clinical manifestations, but suggests that the approach must be to the prevention and cure of the underlying atherosclerosis. *Adrian V. Adams*

EPILEPSY

491. **The Treatment of Epilepsy with Primidone (5-Phenyl-5-ethylhexahydropyrimidine-4 : 6-dione).** (Le traitement de l'épilepsie par la primidone (5 phényl-5 étylhexahydropyrimidine-4-6 dione))

J. DELAY, G. TEULIÉ, R. MARTY, M. GUIBERT, and J. PERSE. *Thérapie* [*Thérapie*] **9**, 411–423, 1954. 1 fig., 22 refs.

The authors report the results of a therapeutic trial of primidone (" mysoline ") in the treatment of 50 cases of epilepsy which were selected for the trial as being all cases of convulsive grand mal associated with mental deterioration necessitating confinement of the patient in hospital. In all cases previous treatment with barbiturates or hydantoinates had been given. As the patients were in hospital their response to treatment could be easily and accurately observed during the 4 months of the trial. Results were compared with those in patients not receiving primidone.

The authors came to the following conclusions. (1) The most efficacious dose of primidone is from 0·75 to 1·75 g. daily. (2) The effect of primidone on the motor manifestations of epilepsy is at least equal to that of barbiturates and hydantoin preparations. (3) The drug improved the psychological manifestations of epilepsy in several cases unresponsive to previous treatment, but its effects were unpredictable. (4) The hypnotic effect of the drug in effective doses is less evident than that of the barbiturates and can be lessened by giving amphetamine. (5) The slight toxic effects, such as somnolence, nausea, and vertigo, noted during the early stages of treatment, disappeared spontaneously and on the whole tolerance was good, particularly from the haematological point of view; no gross symptoms of intolerance were seen. (6) There was improvement in the electroencephalogram, which coincided with clinical improvement, particularly in patients with grossly abnormal tracings, and an over-all stability of the tracings when the clinical results were equal to those obtained by previous treatment. (7) Psychometric measurements

showed that during a period of 3 months 24 patients treated with barbiturates and hydantoinates showed slightly more deterioration than 30 of the patients receiving primidone. Comparison with the control group showed that the results with primidone were better in 8 cases, about the same in 34, and less good in 8.

J. MacD. Holmes

492. **Combined Drug Therapy in Petit Mal Epilepsy**
D. CHAO and W. S. FIELDS. *Journal of Pediatrics* [*J. Pediat.*] **45**, 293–296, Sept., 1954. 4 refs.

Results obtained with "milontin" (N-methyl-α-phenylsuccinimide), alone and in combination with "tridione" (troxidone), in the treatment of petit mal epilepsy are reported from Baylor University College of Medicine, Houston, Texas. To 15 children with petit mal epilepsy, 11 of whom had been previously treated with other drugs, milontin was given in a dosage of 0·5 g. three times a day, increased after one week to 1 g. three times a day. This drug, when given alone, was effective in only 3 of the patients; in the remainder it caused toxic reactions when the dosage was raised to anticonvulsant level. Milontin in small doses combined with tridione was more effective in controlling seizures than either drug given independently. *L. Crome*

493. **Psychomotor Epilepsy in Children.** (Epilepsia psicomotriz en el niño)
A. GAREISO and M. TURNER. *Archivos argentinos de pediatría* [*Arch. argent. Pediat.*] **41**, 311–341, June, 1954. 13 figs., 23 refs.

The authors describe 36 cases of psychomotor epilepsy with onset in childhood. The patients' ages ranged from 20 months to 21 years, but the great majority were aged between 4 and 14; in all the older patients the illness had started before the age of 7. In 11 cases there was a family history of psychiatric disturbance, mainly epileptic, while in 25 there was evidence of head injury during or after birth and in 5 of these a history of infection of the central nervous system. Cephalic and abdominal sensations, such as pain, constriction, or a feeling of heaviness, were observed in many cases, and the authors consider that the patient's subjective account furnishes valuable aid in the attempt to locate the focus.

The most frequent motor phenomena were clonic jerks and twitchings, torsion and rotational movements, and various motor automatisms of different kinds, mainly oral. Vasomotor changes, diarrhoea, vomiting, and other autonomic symptoms were present in many cases. Grinding of the teeth, sleep-walking and talking, and night terrors were frequently observed and are considered as evidence of psychomotor phenomena occurring during sleep. The authors claim to be able to differentiate several patterns from this great wealth of symptoms and signs.

In most of the cases the electroencephalogram showed evidence of an irritative focal disturbance which, contrary to the findings of other authors, was not confined to the temporal lobe, but spread to other areas. Slow, unstable rhythms were also frequent. Drug treatment was successful in 21 cases, barbiturates and phenytoinum sodium being the most effective [but the form of treatment is not described in sufficient detail and no adequate statistics are given]. *Richard de Alarcón*

CRANIAL NERVES

494. **"Gangliolysis" for the Surgical Treatment of Trigeminal Neuralgia**
A. STENDER. *Journal of Neurosurgery* [*J. Neurosurg.*] **11**, 333–336, July, 1954. 1 fig., 10 refs.

An operation which the author terms "gangliolysis" is described for the treatment of trigeminal neuralgia. This operation, which is a modification of that proposed by Taarnhøj (*J. Neurosurg.*, 1952, **9**, 288), consists in exposing the trigeminal ganglion by an extradural approach in the usual way. When the dura mater has been stripped from the 3rd and 2nd divisions of the nerve the ganglion and its root are laid bare and the membrane covering the ganglion is then removed. No further operative interference with the ganglion is carried out; as a result there is no consequent sensory deficit, yet it is claimed that by this method the attacks of neuralgia are relieved.

The author has performed this operation at the West-end Hospital, Berlin, in 18 cases in a recent period of 13 months and in all cases the pain was abolished for a considerable postoperative period. Some early cases relapsed, probably because of failure to open Meckel's cave, and this procedure is therefore now carried out in all cases. The follow-up period is considered to be still too short and hence no detailed results are presented. The aetiology of tic douloureux is discussed and the suggestion made that it may be due to attacks of vascular spasm in the ganglion causing paroxysmal local ischaemia. The beneficial effects of this operation are thus ascribed to the effect of removing the vasomotor nerves and hence inducing a resultant hyperaemia.

Donald McDonald

495. **The Nature of Bell's Palsy**
R. WYBURN-MASON. *British Medical Journal* [*Brit. med. J.*] **2**, 679–681, 18 Sept., 1954. 7 refs.

A short account is given of the connexions between the great auricular nerve and the facial nerve. This is followed by clinical details of cases in which facial palsy occurred in association with herpes zoster, tic douloureux, a gunshot wound of the great auricular nerve, *x*-irradiation, alcohol injection of the great auricular nerve, fracture of the odontoid process, and a tumour of the medulla. On the basis of the association in these cases the author concludes that antidromic impulses passing along branches of the auricular nerve irritate the facial nerve in such a way as to produce swelling, inflammatory changes, and subsequent paresis.

Proceeding on this assumption he treated 20 successive cases of Bell's palsy, in which there were pain and paraesthesiae as well as paresis, by infiltration of the great auricular nerve with 2% procaine. There was immediate and complete relief of pain and paraesthesiae. This suggested that the sensory disturbance in cases of

Bell's palsy must be the result of a disturbance—a "neuritis"—of the great auricular nerve, set up in some cases by exposure of the side of the neck to cold or damp. The author concludes, therefore, that in a large proportion of cases Bell's palsy is a result of a neuritis or irritation of the great auricular nerve.

[There are certain obstacles to the immediate acceptance of this concept. In some of the cases quoted it seems quite probable that both the facial and the great auricular nerves could have been damaged by the noxious agents concerned. Moreover, the view that antidromic impulses may produce oedema and "neuritis" in another nerve seems to require a little more support.]

L. A. Liversedge

NEUROMUSCULAR DISEASES

496. **Pyridostigmin (Mestinon) in the Treatment of Myasthenia Gravis**

R. S. SCHWAB and W. H. TIMBERLAKE. *New England Journal of Medicine* [*New Engl. J. Med.*] **251**, 271–272, Aug. 12, 1954. 3 refs.

"Pyridostigmin" ("mestinon") is an analogue of neostigmine having one-fourth the anti-myasthenic effect of neostigmine, but with the advantage of not causing gastrointestinal side-effects. This paper records a clinical trial of mestinon carried out at the Massachusetts General Hospital (Harvard Medical School), Boston, on 50 patients with myasthenia gravis. Of these, about a third noticed no difference in effect between mestinon and neostigmine, 14 thought mestinon to be less effective, and 20 found the drug superior to neostigmine because of the lack of intestinal stimulation, so that they did not have to take belladonna drugs.

The authors point out that a frequent disadvantage of neostigmine is the need to take atropine to counteract its gastrointestinal side-effects, which not only makes it less easy to recognize the symptoms of overdosage of neostigmine, but may prevent its use by a number of patients who are sensitive to repeated doses of atropine. On the other hand, these side-effects of neostigmine may provide a useful early warning of overdosage in patients who do not normally suffer from them, and such patients taking mestinon must therefore be watched with special care for other signs of toxicity.

N. S. Alcock

497. **Mestinon in Myasthenia Gravis. Preliminary Report**

J. E. TETHER. *Diseases of the Nervous System* [*Dis. nerv. Syst.*] **15**, 227–231, Aug., 1954. 19 refs.

"Mestinon" ("pyridostigmin"), an analogue of neostigmine, was used at the Indiana University Medical Center, Indianapolis, in the treatment of 56 patients (13 males, 43 females) with myasthenia gravis, 50 mg. of mestinon being given in place of each 15 mg. of neostigmine, the daily dose of which ranged from 30 to 2,700 mg., with an average of 345 mg. Equally good control of the myasthenia was obtained with mestinon, the effect of which was smoother and more sustained than that of neostigmine. In several instances in which mestinon was at first thought to be inferior to neostigmine, adjustment of the dosage showed it to be more effective.

The incidence of untoward reactions was considerably less with mestinon than with neostigmine, and the author is convinced that, except for the slower onset of its effect, the former is the more useful drug.

[American and British experience of myasthenia seem to be rather at variance. The author states that he has seen 456 cases in the last 12 years and that the dosage of neostigmine employed ranges up to 3,750 mg. a day —both figures being remarkably high. It also seems surprising that in discussing the management of myasthenia, no mention is made of thymectomy.]

N. S. Alcock

498. **The Treatment of Myasthenia Gravis with a Homologue of Neostigmine, "Mestinon".** (Behandling af myasthenia gravis med et prostigminhomolog: Mestinon)

L. ENGBÆK. *Ugeskrift for Læger* [*Ugeskr. Læg.*] **116**, 1252–1254, Sept. 2, 1954. 7 refs.

The results of the treatment of 10 myasthenic patients with "mestinon" ("pyridostigmin") are reported from the Rigshospital, Copenhagen. This substance has an action similar to, but weaker than, neostigmine in antagonizing curare and inhibiting cholinesterase in isolated muscle, and it also resembles neostigmine in increasing the height of contractions in maximally stimulated muscle, although this action is weaker and slower but more prolonged than that of neostigmine. Previous clinical reports agree that the action of mestinon in man is more long-lasting than that of neostigmine, but opinions on its effect in relieving symptoms of myasthenia gravis have differed.

Of the present author's 10 patients, 2 derived no benefit from mestinon, 2 were improved temporarily but preferred to return to treatment with neostigmine, 5 were stabilized on regular doses of mestinon (one taking neostigmine in addition), and one seemed to benefit from a short trial with mestinon but died later following thymectomy. Side-effects on the autonomic nervous system, such as gastrointestinal upset, were less with mestinon, and the author is of the opinion that a proportion of mild and moderately severe cases of myasthenia gravis obtain an advantage from this and from the more prolonged action of the drug. Some patients prefer the more pronounced action of neostigmine, and for these a combination of this drug with mestinon is recommended.

J. B. Stanton

499. **Ribosuria in Muscular Dystrophy**

J. N. WALTON and A. L. LATNER. *Archives of Neurology and Psychiatry* [*Arch. Neurol. Psychiat.* (*Chicago*)] **72**, 362–364, Sept., 1954. 7 refs.

A test for ribosuria, as described by Orr and Minot, was carried out on specimens of urine from 89 cases of myopathy and gave a positive result in 12 (13·5%); ribosuria was also discovered in samples from 2 cases of motor neurone disease. It is concluded that a test for the detection of ribosuria is of no value in the diagnosis of myopathy.—[Authors' summary.]

Psychiatry

500. **Symptoms of Anxiety and Tension and the Accompanying Physiological Changes in the Muscular System**
P. SAINSBURY and J. G. GIBSON. *Journal of Neurology, Neurosurgery and Psychiatry* [*J. Neurol. Neurosurg. Psychiat.*] **17**, 216–224, Aug., 1954. 3 figs., 5 refs.

In 30 anxious and tense patients an inventory was made out recording their symptoms, their feelings (anxiety, tension, etc.), and their bodily complaints ascribable to muscular over-activity (head sensations, backache, etc.). The incidence of these complaints was shown.

A direct measure of the muscle tension of these patients was obtained by electronically summing the action potentials in the frontalis, forearm extensors, and, in some, the neck muscles, while they relaxed. Reliable scores were obtained. The patients were divided into two groups: those whose symptom scores on the inventory were above and those who were below the median. The muscle tension scores of the former were significantly higher in both the arms and forehead. Those with the most clinical manifestation of anxiety and tension, therefore, were the more muscularly over-active. The patients were divided into those with and those without head, neck, or arm symptoms; the former showed significantly higher muscle tension in the relevant muscle. The onset of headache during recordings was accompanied by significant increases in the innervation of the frontalis muscle. Bodily symptoms attributable to a generalized alteration in muscular innervation, such as tremor and startle, were accompanied by significant increases in muscle activity in well-separated areas.

A significant concordance between four distinct muscle groups suggested that the body musculature as a whole receives increased innervation in patients who are anxious.—[Authors' summary.]

501. **The Fractionation of Urinary Neutral 17-Ketosteroids from Chronic Male Schizophrenics**
M. REISS and S. R. STITCH. *Journal of Mental Science* [*J. ment. Sci.*] **100**, 704–710, July, 1954. 1 fig., 18 refs.

The urinary excretion of fractionated 17-ketosteroids of patients with schizophrenia was estimated and compared with that of healthy subjects. The patients were suffering from various forms of schizophrenia, except catatonia, and the duration of stay in hospital ranged from one year to 26 years. Members of the laboratory staff acted as controls.

In normal subjects Peak No. 3 in the chromatograph pattern, representing androsterone, was higher than Peak No. 5, representing a mixture of androst-5-en-3β-ol-17-one and teston-3α-ol-17-one, whereas the converse was the case in schizophrenics. Furthermore, the excretion of androsterone was higher and the excretion of the Peak-5 substances was lower in controls than in the schizophrenics. The age of the patient and duration of stay in hospital did not significantly influence ketosteroid excretion.

It is emphasized that the differences observed are not necessarily specific for schizophrenia; fractionated 17-ketosteroid excretion in other diseases is being investigated. *Adrian V. Adams*

502. **Schizophrenic-like Psychotic Reactions with Administration of Isoniazid**
W. S. WIEDORN and F. ERVIN. *Archives of Neurology and Psychiatry* [*Arch. Neurol. Psychiat.* (*Chicago*)] **72**, 321–324, Sept., 1954. 7 refs.

The occurrence of toxic psychoses, with certain features resembling those of schizophrenia, is reported in 5 patients under treatment with isoniazid or iproniazid in combination with other antituberculous drugs at the Charity Hospital of Louisiana, New Orleans. In all cases the dosage was within the normal therapeutic range and the possibility of tuberculous meningitis had been carefully excluded.

Prodromal symptoms were restlessness, insomnia, anxiety, and paraesthesiae, with an increased sensitivity to auditory and visual stimuli. Insight was lost early, none of the patients interpreting the prodromal symptoms as untoward and none being able to record details of the psychotic episode after recovery. Following the prodromal stage, illusory experiences and ideas of reference with paranoid features became prominent. [It is difficult to agree with the authors that the desire of one patient to leave hospital because " she blamed isoniazid for her predicament " was necessarily a psychotic manifestation.] The full psychotic picture included aural hallucinations in all patients, visual hallucinations in one, and disorientation of varying degree. Withdrawal of the drugs was soon followed by improvement in the psychomotor and sensory disturbances, but delusions and hallucinations were slower in disappearing, while anxiety and the finer affective changes, if they improved at all, were the last to do so. It is suggested that this type of psychotic reaction is more likely to occur in patients who already show prepsychotic adaptation, and that the appearance of prodromal symptoms in a definite sequence may be of some value in enabling its possible occurrence to be predicted. *Adrian V. Adams*

503. **Psychiatric and Neurological Side-effects of Isoniazid and Iproniazid**
H. PLEASURE. *Archives of Neurology and Psychiatry* [*Arch. Neurol. Psychiat.* (*Chicago*)] **72**, 313–320, Sept., 1954. 33 refs.

This report is based on observations made on 602 psychiatric patients under treatment for tuberculosis with isoniazid (4 mg. per kg. body weight per day) and streptomycin (1 g. intramuscularly every 3 days) at Pilgrim State Hospital, Edgewood, New York, between March, 1952, and March, 1954. This total included some 200 patients transferred from tuberculosis hospitals

in New York City and Nassau and Suffolk Counties as having developed psychoses requiring certification, about half of whom had received isoniazid or iproniazid or both. None of the patients treated at Pilgrim State Hospital developed new psychotic symptoms during isoniazid therapy, although agitated episodes occasionally occurred. Among those transferred from elsewhere there was unequivocal evidence of a toxic psychosis in a few cases only, characterized by fairly sudden onset after a period of drug therapy, clouded sensorium, and aural and visual hallucinations; however, there were several cases in which one of the functional group of psychoses appeared to be related to the administration of isoniazid or iproniazid, clearing up quickly after its discontinuance, the total number of cases of both types being 25.

Among the psychotic patients treated with isoniazid, interruption because of toxicity was necessary in only 5 cases—in 3 because of epileptiform attacks and in 2 because of peripheral neuropathy. It seems that isoniazid, even in therapeutic doses, has an aggravating effect on post-traumatic epilepsy and other conditions in which organic brain damage has resulted in a tendency to convulsive attacks. Phenobarbitone is usually—but not always—an effective antidote in such cases. The peripheral neuropathy sometimes induced by isoniazid, although rare, is potentially serious because improvement tends to be extremely slow and is not hastened by intensive vitamin therapy. It is, however, usually mild when normal therapeutic doses are given. It appears to be a different entity from the neuropathies of alcohol poisoning or of aneurin deficiency. Indeed alcoholism, even if accompanied by neuropathy, does not seem to contraindicate the use of the drug. Nor is there any evidence that isoniazid is dangerous in the presence of advanced arteriosclerotic changes. *Adrian V. Adams*

TREATMENT

504. **A Study of the Rationale of the Treatment of Delirium Tremens with Adrenocorticotropic Hormone. 1. The Eosinophil Response of Patients with Delirium Tremens, after a Test with ACTH. 2. Clinical Correlations to Responsiveness to ACTH in Delirium Tremens**
M. Owen. *Quarterly Journal of Studies on Alcohol* [*Quart. J. Stud. Alcohol*] **15**, 384–386 and 387–401, Sept., 1954. 12 refs.

In these two papers the rationale of the treatment of delirium tremens with ACTH is discussed with reference to the results obtained in 27 cases admitted during a 4-month period to the Grasslands Hospital, Valhalla, New York. The author's object in the first part of the investigation was to test the theory that alcoholism is due to exhaustion of the adrenal gland. On the principle that adrenocortical reserve can be assayed by the percentage fall in the number of circulating eosinophils, each patient was given 25 mg. of ACTH intramuscularly, the eosinophil count being determined before and 4 hours after the injection. There was a decrease of 50 to 78% in 14 cases and 0 to 43% in 13, from which it is concluded that adrenocortical insufficiency is not a necessary accompaniment of delirium tremens, and that the action of ACTH is not specific.

In the second paper the author attempts to clarify the alleged effectiveness of ACTH in delirium tremens by correlating the above findings with the phenomena and the patient's history and personality patterns. In a few cases post-mortem findings were also noted. In most of the patients delirium tremens was complicated by intercurrent disease—such as cirrhosis of the liver, pyuria, and pulmonary tuberculosis—and by fever, tachycardia, and hypotension. Details, including the hallucinatory phenomena, are given for each case. It was found that adequate adrenal cortex reserve was significantly commoner in patients who had been alcoholics for less than 15 years than in those who had been alcoholics for 15 to 30 years. Further, there was a significantly greater proportion of patients with adequate adrenal cortex reserve among the group who remained oriented throughout the delirium than in the group who did not, and among those with tuberculosis as compared with those without. The highest degree of correlation was found with auditory hallucination of short duration.

In a well-reasoned discussion the author suggests that prolonged alcoholism produces a pituitary–hypothalmic disorder to which adrenal cortex insufficiency in delirium tremens is secondary, and concludes that the cause is more complicated than simple metabolic dysfunction. Further methods of investigating the psychological and biological factors involved are indicated.

R. J. Matthews

505. **Dangerous Cardiac Effects of Tetraethylthiuram Disulfide (Antabuse) Therapy in Alcoholism**
E. S. McCabe and W. W. Wilson. *Archives of Internal Medicine* [*Arch. intern. Med.*] **94**, 259–263, Aug., 1954. 2 figs., 8 refs.

In order to investigate the severe circulatory reaction which they had observed in alcoholic subjects undergoing treatment with tetraethylthiuram disulphide (disulfiram) (and which had resulted in death in 2 cases reported by other workers) the authors followed up 20 patients (15 men and 5 women) for over one year. All were in the fourth or fifth decade of life and showed no gross abnormalities on physical or laboratory examination. Tetraethylthiuram disulphide was given in a dosage of 1 g., daily for 2 days, followed by an average dose of 0·5 g. daily thereafter. If indicated by the individual response to alcohol testing, the maintenance dose was subsequently raised or lowered. The first test, using 40 ml. of 100% proof whisky, was carried out on the 6th day of therapy, and the second test, in which 20 ml. of 100% proof whisky was given, on the 16th day. Subsequent tests with the latter dose were given as the progress of the patient warranted. The patient's reactions were noted, and electrocardiograms were taken before the test and at the height of the reaction to alcohol.

In the electrocardiogram taken at the height of the test reactions latent coronary insufficiency, as manifested by a total depression or deviation of more than 3 mm.

of S–T segments in all 4 leads, was found in 4 patients; in 3 additional patients, including 2 women, there was inversion of the T waves. Clinically, the alcohol–tetraethylthiuram disulphide reaction is characterized by a facial flush and tachycardia, accompanied by a slight elevation in blood pressure and widening of the pulse pressure. The height of the reaction occurs within 20 to 30 minutes and is dissipated within three-quarters of an hour. In 5 of the 7 cases exhibiting electrocardiographic evidence of myocardial anoxia there was a fall in the blood pressure resulting in a condition resembling shock. In 4 cases there was a considerable degree of nausea and vomiting and a sense of constriction at the lower end of the sternum. In view of the fact that 7 (35%) of the patients in this series showed evidence of dangerous cardiac embarrassment following alcohol–tetraethylthiuram disulphide testing, it is concluded that all such patients should be exhaustively studied from the cardiac standpoint before the institution or continuation of tetraethylthiuram disulphide therapy. Conditions contraindicating the use of this treatment are diabetes mellitus, hepatic, renal, and severe cardiovascular disease, and epilepsy. *Robert Hodgkinson*

506. **Lung Abscess as a Complication of Shock Therapies**
P. WAYL and J. RAKOWER. *Thorax* [*Thorax*] **9**, 216–221, Sept., 1954. 8 figs., 27 refs.

507. **Correlations between Changes in Mental States and Thyroid activity After Different Forms of Treatment**
M. REISS. *Journal of Mental Science* [*J. ment. Sci.*] **100**, 687–703, July, 1954. 1 fig., 18 refs.

In 450 patients suffering from various mental disorders at Barrow Hospital, Barrow Gurney, Bristol, thyroid function was assessed by the radioactive-iodine (^{131}I) technique before and after different forms of treatment had been administered.

In 96% of patients whose thyroid function was below normal before treatment there was an improvement in the mental state afterwards and thyroid function had returned to within normal limits; in 88% of patients whose mental state did not improve after treatment thyroid function remained unchanged or had deteriorated. Of the patients with increased thyroid activity before treatment, a significantly higher proportion improved mentally when thyroid activity fell to within the normal range than when it was unchanged or had increased still further. The difference was still statistically significant when thyroid function changed towards, but had not reached, normal. Furthermore, the mental state of patients whose thyroid function was normal before treatment rarely improved if thyroid activity had increased or decreased when treatment was completed. In patients receiving no special treatment a correlation was observed between spontaneous improvement in the mental state and the return to normal of thyroid activity.

Statistical analysis of the findings indicated that the probability of recovery was greater in patients whose thyroid function had reached normal limits when treatment was completed than in those whose thyroid activity was above or below the normal range. The correlation between changes in mental state and thyroid function appeared to be independent of the particular psychiatric disease or the method of treatment, and the implications of these observations are discussed on the hypothesis that changes in thyroid activity are but one manifestation of complex changes in hormone equilibrium.

Adrian V. Adams

508. **Effect of Chlorpromazine on the Behaviour of Chronically Overactive Psychotic Patients**
J. ELKES and C. ELKES. *British Medical Journal* [*Brit. med. J.*] **2**, 560–565, Sept. 4, 1954. 12 refs.

The authors have investigated the effects of administering chlorpromazine (" largactil ") to a group of 27 (12 male and 15 female) chronically overactive psychotic patients with various types of mental disorder. The patients acted as their own controls, the drug and a similar but inert preparation being given in alternate periods of varying length. Observations of the patients' behaviour, made by a number of independent observers only one of whom knew which patients were receiving the drug, were collated to arrive at the final conclusions. An effective dosage was found after trial to be 150 mg. daily and an adequate period of continuous administration to be 6 weeks at a time.

The results showed that 7 of the patients were " definitely improved " and 11 " slightly improved " in terms of lessened overactivity and improved social habits; in many cases improvement was not apparent until between 3 and 6 weeks after medication was started. The patients suffering from affective disorders appeared to respond rather better than did schizophrenic patients; 9 of the patients in the " improved " groups showed an increase in weight, probably due to improved eating habits. Apart from one case of transient jaundice and 2 showing changes in blood-cell counts the drug was well tolerated. It is suggested that chlorpromazine is worthy of further trial. *J. B. Stanton*

509. **Chlorpromazine and Insulin in Psychiatry**
N. P. LANCASTER and D. H. JONES. *British Medical Journal* [*Brit. med. J.*] **2**, 565–567, Sept. 4, 1954. 11 refs.

The authors describe the effect of the drug chlorpromazine on the " anxiety state " produced by insulin-induced hypoglycaemia, and assess the usefulness of the drug when combined with insulin in the treatment of 31 psychoneurotic patients, it having been first confirmed that chlorpromazine did not influence the action of insulin in lowering blood sugar levels. They found that the palpitation and tachycardia which occur in the hypoglycaemic state were increased, but that sweating, flushing, restlessness, epigastric discomfort, and tremor (all of which are factors in the " anxiety quotient ") were diminished when chlorpromazine was given together with insulin. They also showed that this combination was useful in controlling refractory patients who did not respond to chlorpromazine alone or to modified insulin treatment alone, and in making more manageable those patients who became excited during standard treatment with insulin-induced coma. *J. B. Stanton*

Dermatology

510. **Clinical Experience with Hydrocortisone Ointment**
F. D. MALKINSON and G. C. WELLS. *British Journal of Dermatology* [*Brit. J. Derm.*] **66**, 300–303, Aug.–Sept., 1954. 4 refs.

The effect of an ointment containing hydrocortisone in the treatment of 71 patients suffering from various dermatoses was investigated at the University of Chicago Clinics. The ointment, which consisted of hydrocortisone acetate (2·5%) in a base of liquid paraffin, yellow soft paraffin, cholesterol, and " multiwax ", was applied very thinly to the affected areas of the skin 3 times a day. In suitable cases the hydrocortisone ointment was applied to lesions on one side of the body and the ointment base alone to similar lesions on the opposite side, the results being then compared.

Particularly good results were obtained in chronic otitis externa, eczematous dermatitis of the eyelids, and in some cases of pruritus ani. In most chronic conditions, despite prolonged suppression of symptoms, withdrawal of hydrocortisone ointment was followed by a relapse. The ointment had no effect upon the development of erythema after exposure to ultraviolet light.

S. T. Anning

511. **Diagnosis, Physiopathology, and Treatment of Acne Vulgaris**
R. ARON-BRUNETIÈRE. *Australian Journal of Dermatology* [*Aust. J. Derm.*] **2**, 114–139, June, 1954. 10 figs., bibliography.

The author restricts the term acne to those eruptions characterized by the presence of comedones, and distinguishes, with Sabouraud, two varieties of acne vulgaris —acne punctata, which is the primary form, with comedones of all sizes and sebaceous microcysts, and polymorphic acne in which there are papules, pustules, and nodules in addition to the comedones. An additional, less well recognized form is " monomorphic acne " in which the eruption consists entirely of microcysts or pustules; this form occurs later than does polymorphic acne, usually after the age of 21. One type may change into the other. Acne vulgaris must be differentiated from the recurrent miliary papulopustular eruption of Brocq, in which minute, itchy, follicular lesions appear in sudden attacks. The vaginal cytology was studied in 83 female patients. In 25 out of 30 (83%) with polymorphic acne there was complete absence, during at least part of the menstrual cycle, of keratinized eosinophilic cells, but this finding occurred in only 32 out of 49 (65%) with monomorphic acne. Urinary excretion of 17-ketosteroids was increased in 20 out of 46 female patients and was very high in 12 of these. The secretion of pituitary gonadotrophin was usually very low in cases of polymorphic acne, but was higher in those of monomorphic acne. The secretion of thyrotrophic hormone as estimated by Aron's method was found to be high in men with acne and in 40% of all patients with monomorphic acne. It is suggested that the primary disorder in acne vulgaris may lie in the level of secretion of the pituitary gonad-stimulating hormones.

In treatment it is important to remember that small and large doses of steroids and of pituitary hormones may have opposite effects. Thus chorionic gonadotrophin is " acnegenic " in large doses, whereas small doses given over longer periods may be beneficial. The form of treatment recommended by the author is the implantation into the subcutaneous tissue of the upper and outer quadrant of the buttock of 1,000 units of serous gonadotrophin. After 2 to 4 days there is a transient exacerbation of the acne followed by steady improvement. This treatment also relieves the constipation which is so common in women (and rare in men) with acne. Dysmenorrhoea is often abolished. Although topical treatment is not always necessary, a peeling ointment is often a useful adjuvant in the management of these cases.

E. Lipman Cohen

512. **Congenital Polykeratosis.** (La polykératose congénitale)
A. TOURAINE. *Presse médicale* [*Presse méd.*] **62**, 1289–1292, Sept. 29, 1954. 12 figs., 4 refs.

From the group of hereditary dermatoses showing dyskeratosis the author isolates a type of polydysplasia which shows a tendency to hyperkeratinization of the skin and its appendages and keratinization of mucous membranes. He goes on to analyse in great detail the various elements of congenital polykeratosis: mucocutaneous, subungual, and follicular. Disturbances of nail growth, sweating, and pigmentation, as well as changes in the hair and teeth and in the patient's mentality, are discussed. Various syndromes combining these changes are mentioned.

[This complex paper should be read in the original by those interested.]

S. T. Anning

513. **Personality and Emotional Factors in Chronic Disseminated Neurodermatitis**
C. E. FISKE and M. E. OBERMAYER. *Archives of Dermatology and Syphilology* [*Arch. Derm. Syph.* (*Chicago*)] **70**, 261–267, Sept., 1954. 3 refs.

A group of 21 patients with chronic disseminated neurodermatitis and a control group of 21 patients with psychiatric disorders were examined and subjected to a series of tests—the Rorschach, the Draw-a-Person, the Thematic Apperception, and the Shipley–Hartford. The results were scored and submitted, together with biographical data but without identifying marks, to three clinical psychologists who judged the material independently and determined from it the presence or absence of each of 39 traits of personality, emotion, or intellect considered to be of significance in neurodermatitis and neuroticism.

Of these traits, 13 were common to both groups, while 9 others were peculiar to the patients with neurodermatitis to a significant extent. These findings suggest that patients with neurodermatitis are a subgroup of the neurotic population. The basic personality structure of the patient with neurodermatitis shows sadistic, destructive, paranoid, and aggressive elements combined with the features of masochism, insecurity, narcissism, sensitivity, dependence, and marked sexual conflict. There is much preoccupation with the skin and its " charge " of erotic feeling.

[The authors' conclusions seem rather top-heavy, being based largely on test results alone rather than on prolonged clinical observation.] *Desmond O'Neill*

514. **Synthetic Antimalarial Drugs in Chronic Discoid Lupus Erythematosus and Light Eruptions**
J. ROGERS and O. A. FINN. *Archives of Dermatology and Syphilology* [*Arch. Derm. Syph. (Chicago)*] **70**, 61–66, July, 1954. 2 figs., 12 refs.

Mepacrine and chloroquine were tried at the Royal Infirmary, Dundee, in the treatment of patients with chronic discoid lupus erythematosus and light-sensitive summer eruptions. Mepacrine was given for 4 to 38 weeks in a dosage ranging from 0·1 g. once a day to 0·1 g. three times a day. Staining of the skin and nausea were noted in patients given this drug. Chloroquine was administered for 3 to 34 weeks in a dosage of 0·25 g. daily for 5 days each week. Side-effects included headache, nausea, blurring of vision, and rashes; in several cases staphylococcal lesions, such as furuncles and sties, developed. No staining of the skin was observed. Both drugs were effective in controlling the eruptions of chronic discoid lupus erythematosus and those of light-sensitive patients. *Kate Maunsell*

515. **Treatment of Dermatoses with Local Application of Hydrocortisone Acetate**
H. M. ROBINSON and R. C. V. ROBINSON. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **155**, 1213–1216, July 31, 1954. 5 refs.

At the University of Maryland School of Medicine, Baltimore, local application of hydrocortisone acetate in the form of a lotion or ointment in strengths of 0·5%, 1%, and 2·5% was tried in the treatment of 418 patients suffering from a variety of dermatoses. It was found that in a strength of 0·5% both lotion and ointment were relatively ineffective, and that in general an oily base was the most suitable vehicle. Hydrocortisone was of value in atopic dermatitis, neurodermatitis, seborrhoeic dermatitis, contact dermatitis, pruritus ani, and pruritus vulvae, but was ineffective in alopecia areata, psoriasis, pityriasis rosea, acne vulgaris, lupus erythematosus, and lichen planus. In patients with acne vulgaris the condition became worse [probably as a result of direct hormonal effect], but other untoward reactions in the series were due to sensitivity to the vehicle. In patients with chronic dermatoses there was a tendency to relapse when the hydrocortisone was discontinued; nevertheless, it is considered that the drug has an important place in the treatment of skin conditions. *H. R. Vickers*

516. **Vesicular Eruptions of the Hands and Feet of Dyshidrotic Type. Clinical and Therapeutical Analysis**
M. G. FREDRICKS and F. T. BECKER. *Archives of Dermatology and Syphilology* [*Arch. Derm. Syph. (Chicago)*] **70**, 107–114, July, 1954. 3 figs., 8 refs.

The causative factors in vesicular eruptions of the hands and feet of the dyshidrotic type are discussed, and the results of treatment in 145 cases seen at Duluth Clinic, Duluth, Minnesota, are described. It was found that in the majority of cases the condition was the result of tension, anxiety, and nervous fatigue. The treatment regimen therefore consisted in a discussion of the causes with the patient and sedation, as well as application of suitable dressings to the affected parts. In addition anticholinergic drugs were given, the most effective being methantheline. *Kate Maunsell*

517. **The Effect of Mepacrine on Light Sensitivity in Lupus Erythematosus**
F. R. BETTLEY and F. PAGE. *British Journal of Dermatology* [*Brit. J. Derm.*] **66**, 287–293, Aug.–Sept., 1954. 6 figs., 2 refs.

The investigation described in this paper from the Middlesex Hospital, London, was undertaken to determine whether the beneficial effect of mepacrine in chronic lupus erythematosus is the result of an increase in tolerance to light. Patients with chronic lupus erythematosus received up to 100 mg. of mepacrine twice a day, and the sensitivity of the skin to light was tested monthly. A commercial " sun lamp " with a filter of cellulose acetate was used to test light sensitivity, a photometer being employed to ensure accuracy of dosage. The minimum erythema dose (M.E.D.) was measured on the skin of the abdomen.

The average M.E.D. in untreated patients with lupus erythematosus was about half the normal. In patients receiving mepacrine the increase in light tolerance was very gradual but the clinical effect on the lesions of lupus erythematosus was more rapid. The authors believe the results indicate that " mepacrine has another action which exerts a more immediate effect on the disease itself than simply by increasing tolerance to sunlight ".

[The conclusions reached would be more impressive if the findings were considered statistically. Averaged results from 5 control subjects and 9 patients with lupus erythematosus after one-half or one-quarter minute's exposure cannot be assessed satisfactorily in any other way.] *S. T. Anning*

518. **Nasal Carriage in Staphylococcal Skin Infections**
L. G. TULLOCH. *British Medical Journal* [*Brit. med. J.*] **2**, 912–913, Oct. 16, 1954. 14 refs.

The author considers that apart from constitutional, metabolic, and immunological factors, recurrence of staphylococcal skin infection is mainly due to the presence of a chronic nasal carrier state in the patient. Evidence in support of this opinion is quoted from the literature, and additional evidence was sought by the author at the Manchester and Salford Hospital for Diseases of the Skin by phage-typing the organisms obtained from the skin lesion and from the anterior nares

in 73 consecutive cases of staphylococcal infection with the following results. In 20 out of 23 cases of sycosis barbae in which the organism could be typed the strains from the nose and skin were of the same type; in 7 cases neither strain was typable. In 18 out of 24 cases of furunculosis and folliculitis the strains were of the same type, and in 9 they were untypable. In 7 out of 8 cases of infective eczematoid dermatitis the strains were identical, and in 2 they were untypable.

It would therefore seem that the nose is a primary source of infecting organisms in most cases of chronic staphylococcal dermatosis, and local treatment to lesions should be supplemented by an attack on the nasal flora. For this purpose 0·1% tyrothricin solution in 10% propylene glycol with 1% sodium mixed alkyl sulphonate, or an aqueous solution of penicillin (1,000 units per ml.), may be administered by means of an atomizer, or a cream containing 0·1% of tyrothricin or 1% of aureomycin may be used. *Ferdinand Hillman*

519. **Erythromycin Therapy of Acne Vulgaris**
J. VAN DE ERVE. *Journal of Investigative Dermatology* [*J. invest. Derm.*] **23**, 67–69, Aug., 1954. 5 refs.

Trial of erythromycin in 60 cases of acne vulgaris of various types resulted in excellent control of the pustular element in nearly all cases. This improvement was temporary in nature with recurrence following in the majority of instances within a month after treatment. There was little or no effect on the sebaceous secretion itself, either in the formation of oil on the skin or as comedones.

Only one patient was intolerant of the drug, manifesting diarrhea to the extent of having to discontinue therapy. No untoward effects, such as monilial overgrowth or disturbance in the bacterial balance, were noted. The drug is apparently safe and is valuable for the control of the pustular phase of acne vulgaris but has little effect on the basic sebaceous overactivity.—[Author's summary.]

520. **Antimycotic Activities of Trichomycin, with Special Reference to the Experimental and Clinical Studies of Trichomycin Ointment.** [In English]
S. HOSOYA, M. SOEDA, S. IMAMURA, K. OKADA, S. NAKAZAWA, and N. KOMATSU. *Giornale italiano di chemioterapia* [*G. ital. Chemioter.*] **1**, 217–230, April–June, 1954. 18 figs., 15 refs.

In this report from the University of Tokyo the effect of a new antibiotic, trichomycin, on mycotic infections of the skin is discussed. Trichomycin, which is derived from *Streptomyces hachijoensis*, has been shown to be effective *in vitro* and in experimental animals against *Trichomonas vaginalis* and *Candida albicans*, and markedly beneficial in *Candida* infections and trichomoniasis of the vagina.

Several ointments containing trichomycin were first tested, the most suitable being a base of equal parts of yellow soft paraffin and polyoxyethylenelauryl ether containing 100,000 trichomonad units of trichomycin per gramme of ointment. This was tried in both experimental dermatomycosis of guinea-pigs and a wide variety of dermatomycoses in human beings. The antibiotic appeared to be very effective against *Trichophyton* infections. In no case did the symptoms become worse, and no irritative reactions followed repeated application. The authors claim that in all cases of mycotic infection of the skin there was considerable improvement, with complete cure in just over half. They noted a marked difference between the effect on dry lesions and that on moist lesions, the latter being cured more rapidly. It is further claimed that trichomycin is the only antibiotic so far discovered which is efficacious against mycotic infection.

[All the published reports on trichomycin have originated in Japan, and have contained the suggestion that it might prove a useful addition to the antibiotics now commonly employed; further work will, however, be needed before this claim can be substantiated.]
R. F. Jennison

521. **The Treatment of Actinomycosis with Penicillin and Sulphadiazine.** (Zur Behandlung der Aktinomykose mit Penicillin und Sulfapyrimidin)
J. CAP. *Dermatologische Wochenschrift* [*Derm. Wschr.*] **129**, 321–325, 1954. 4 figs., 18 refs.

In this paper from the University Skin Clinic, Heidelberg, 4 cases of cervico-facial actinomycosis are fully described. They were treated with penicillin combined with sulphadiazine and responded in 4 to 6 weeks. The most effective regimen consisted in giving 1 g. of sulphadiazine thrice daily and 1 mega unit of penicillin every 2 days to a total of 93 to 130 g. of the former and 18 mega units of the latter. *H. R. Vickers*

522. **Follicular Lymphoma of the Skin.** [In English]
J. O'D. ALEXANDER and T. PASIECZNY. *Dermatologica* [*Dermatologica (Basel)*] **109**, 1–13, July, 1954. 6 figs., 16 refs.

From Glasgow Royal Infirmary 4 cases of lymphocytoma cutis (or " follicular lymphoma " as the authors prefer to name the condition) are described. This condition presents two distinct clinical types. In one type there are multiple, infiltrated, brownish papules on the face and neck which may itch and are often related to photosensitivity. In the other type there are solitary elevated tumours, up to 2 or 3 cm. in diameter, on the face, ear-lobes, forearms, or scrotum. Both types are radiosensitive. The authors compare this condition with " Brill's disease " and suggest that the two conditions are probably related, although their histological pictures are not identical.

[The authors introduce much confusion into the nomenclature. Follicular lymphoma, or Brill–Symmers disease, is a primary malignant tumour of the reticuloendothelial system related to lymphosarcoma and the lymph nodes are enlarged. In the abstracter's opinion the use of the term " follicular lymphoma " as the title for a paper on lymphocytoma cutis is unjustifiable. Moreover, when the authors mention Brill's disease (a form of typhus seen in the U.S.A.) they mean to refer, presumably, to Brill–Symmers disease.]
S. T. Anning

Paediatrics

INFANT FEEDING

523. **Birth Weight and the History of Breast-feeding**
J. W. B. DOUGLAS. *Lancet* [*Lancet*] **2**, 685–688, Oct. 2, 1954. 3 refs.

The author, writing from Edinburgh University, describes an observation made during a long-term study of child health—namely, that the proportion of underweight infants (less than 6 lb. (2·7 kg.)) born to multiparae is inversely related to the duration of breast-feeding of previous siblings.

The birth weights of 1,697 infants were recorded and related to the age at weaning of the previous sibling. It was found that the mean birth weight of these infants and the proportion weighing less than 6 lb. at birth varied according to the age at weaning of the previous infant, and that with a reduction in the duration of breast-feeding there was, correspondingly, a reduction in the mean birth weight of subsequent children. The mean birth weight rose unevenly with increasing success in the feeding of previous siblings, this rise being accompanied by a steep decline in the proportion of children weighing less than 6 lb. at birth.

In order to determine whether any other factor played a part, the infants were further grouped according to sex, the social status of the parents, prematurity of previous siblings, maternal age, birth spacing in the family, and maternal employment. None of these factors appeared to influence the relationship between low birth weight and early weaning of the previous infant, although the proportions of underweight infants in these various groups differed.

Finally, to determine whether success in breast-feeding was part of a generally good reproductive performance the mothers were divided into two groups—those who ceased breast-feeding because of milk failure, and those who voluntarily ended a well-established lactation. It was found that the proportions of underweight infants in these two groups were similar. *E. M. Watkins*

524. **Clinical and Chemical Studies in Human Lactation. VIII. Relationship of the Age, Physique, and Nutritional Status of the Mother to the Yield and Composition of Her Milk**
F. E. HYTTEN. *British Medical Journal* [*Brit. med. J.*] **2**, 844–845, Oct. 9, 1954. 2 figs., 17 refs.

The author studied the adequacy of lactation in relation to the age, height, general physical health, net change in weight during pregnancy, and diet during pregnancy of 155 primiparous patients attending at Aberdeen maternity clinics. At the first antenatal visit a record was made of the patient's general state of health, and of her height and weight. (Since the "net weight change" for the purpose of this study was defined as the difference between the weight on the day of discharge from hospital and the weight at or before the 14th week of pregnancy, this figure was available only for the 110 patients who first attended within the first 14 weeks.) A diet survey was carried out in 55 cases during the 7th month of pregnancy over a period of one week.

The milk yield, measured on the 7th day post partum, tended to be lower in the older patients, only 19% of those aged 28 or over having a yield of 450 ml. or more, whereas in the age group 16 to 19 the proportion was 55%. The yield also tended to be lower in those who made a large net weight gain during pregnancy, a yield of 500 ml. or more being obtained in less than 20% of the group gaining 10 lb. (4·5 kg.) or more, and in 35% of the group gaining 3 lb. (1·36 kg.) or less. The fat content of the milk was not related to either age or weight gain. Well-grown women and those of good physique generally gave a higher yield of milk with a higher fat content than the average, but the difference was neither consistent nor statistically significant. No relation could be found between milk yield and diet.

It is pointed out that milk yield depends on the amount of secretory tissue in the breast; this is closely related to the degree of enlargement occurring during pregnancy, which varies widely, and diminishes with increasing age at the first pregnancy. In about one-third of cases the yield appeared to be inadequate, and it is suggested that if this finding is generally applicable "then some modification of existing attitudes to breast-feeding and its management is called for".
Elaine M. Osborne

525. **Artificial Feeding and Energy Requirements of Young Infants**
F. E. HYTTEN and I. A. G. MACQUEEN. *Lancet* [*Lancet*] **2**, 836–839, Oct. 23, 1954. 7 figs., 9 refs.

Inquiries made by the Aberdeen City Health and Welfare Department having suggested that many infants were not thriving on dried-milk mixtures as recommended by maternity and child-welfare clinics, it was decided to investigate the chemical composition of such mixtures. In a preliminary study feeds suitable for infants of four different weights were made up in the laboratory from the appropriate grade of National dried milk according to the instructions on the tin and using the official measure. The calorie value of the feeds varied very considerably, depending upon whether the scoop was simply dipped into the powder or was tightly packed before being levelled off, but in almost all cases, whichever way prepared, it was below the optimum level of 120 Cal. per kg. (55 Cal. per lb.) body weight, and in some instances was less than 90 Cal. per kg. Samples of milk mixtures were then collected by health visitors from 100 homes where a baby aged less than 3 months was being fed entirely on such a mixture. There was

no conscious selection of cases, in no instance was a feed specially prepared, and no mother had been warned that a sample might be taken. The range of variation in fat, protein, lactose, and sucrose content of these feeds, in the proportion of total calories derived from carbohydrate, and in the total daily intake of calories per kg. is shown in a series of diagrams.

Four infants in this series were receiving less than 110 ml. of water and one less than 95 ml. per kg. daily. In 9 cases the daily intake of protein was less than 3 g. per kg. and was associated with a very low calorie intake. The daily calorie intake fell below the theoretical requirement of 120 Calories per kg. in 69 instances, and in 49 it was below 100 Calories per kg. The proportion of babies who thrived was significantly lower in this last group than in the remainder, and it is emphasized that the babies whose intake was exceptionally high showed no ill effects, the healthy infant apparently having a greater capacity for digesting and utilizing food than is commonly supposed. Further analysis confirmed the widely held clinical impression that the malnourished child has an increased susceptibility to infection, irrespective of housing conditions, type of feeding, and intelligence of the parents. Some reduction in infant morbidity might thus reasonably be expected to follow the elimination of under-nutrition.

The primary reason for the high incidence of low-calorie feeding seems to be in the instructions given to mothers. The use of National dried milk reconstituted to the strength of whole milk (one scoopful per fluid oz. (28 ml.) of water) with added sugar would give the average baby about 130 Calories per kg. daily. Any "overfeeding" resulting from this would do no harm and the likelihood of underfeeding would be considerably reduced. *Jas. M. Smellie*

NEONATAL DISORDERS AND PREMATURITY

526. **The Effects of Hypoxia on the Respiration of Newborn Infants**
H. C. MILLER and F. C. BEHRLE. *Pediatrics* [*Pediatrics*] **14**, 93–103, Aug., 1954. 4 figs., 22 refs.

This paper records further investigation of the physiology of respiration in the neonatal period carried out at the University of Kansas Medical School, Kansas City. In their earlier studies (*Pediatrics*, 1953, **12**, 141; *Abstracts of World Medicine*, 1954, **15**, 350) the authors recorded the respiratory movements of the chest and abdominal wall in a large series of newborn infants and concluded that three distinct phases of respiratory activity could be distinguished. During the first phase, which lasts for about one hour after birth, extra-uterine respiration is being established; in the second phase, of 1 to 24 hours' duration, there is a regular respiratory rhythm, with synchronous expansion and contraction of the chest and abdominal walls; this is followed by a third phase in which the respiratory rhythm is often grossly irregular and the chest and abdominal movements asynchronous. In the present study the authors set out to discover the reasons for these variations in respiratory pattern.

The full-term, healthy infants used in the tests were placed in a plethysmograph to which a spirometer was fitted, and while gas mixtures containing 10 or 12% of oxygen were administered for periods of 5 to 8 minutes the changes in minute volume were recorded. In 10 infants who were observed during the first 24 hours after birth the average minute volume decreased during the first minute and continued to fall throughout the period of observation. In 10 infants aged 6 to 11 days the minute volume rose slightly during the initial 2 to 3 minutes of oxygen administration and then declined, but not so markedly as in the younger infants. In 10 infants aged 16 to 48 days the minute volume rose higher than in the previous group, and the response to 10% oxygen was greater than that to 12% oxygen. At the end of the test period the infants were returned suddenly to room air, this resulting in a gradual return of minute volume, respiratory rate, and tidal air to the initial values. The incidence of periodic breathing, which was also observed, was found to increase during hypoxia in infants in the older age groups.

From these observations the authors conclude that the chemoreceptor reflexes which arise in the carotid body and aortic arch are relatively weak at birth, but gradually increase in strength during the weeks that follow. These conclusions are supported by the work of a number of other investigators who have reported the finding of weak reflexes before birth, associated with, and probably controlled by, the low oxygen saturation of foetal blood. Evidence has also been advanced which suggests that before birth metabolic processes involving the respiratory centre may be anaerobic in type. The authors suggest that this anaerobic type of metabolism explains the relative inability of hypoxia to induce periodic breathing in infants within a few hours of birth, but that with the change from anaerobic to aerobic metabolism the response to hypoxia becomes increasingly obvious. *R. M. Todd*

527. **Effect of High Concentrations of Carbon Dioxide and Oxygen on the Respiration of Fullterm Infants**
H. C. MILLER. *Pediatrics* [*Pediatrics*] **14**, 104–113, Aug., 1954. 5 figs., 19 refs.

In this investigation into the effect of carbon dioxide on respiratory activities in full-term infants the author employed the same methods as those used in the related studies described above [see Abstract 526]. In two groups of infants, the first consisting of babies of 2 to 24 hours and the second of babies of 6 to 60 days, the comparative effects of 5% carbon dioxide and 100% oxygen on respiratory activity were observed. In the infants aged up to 24 hours the increase in minute volume after exposure for 5 minutes to an atmosphere containing 5% carbon dioxide was 18 times greater than that observed after administration of 100% oxygen, while in the older age group 5% carbon dioxide caused an increase 7 times as great as that following oxygen. The older infants, however, showed a greater increase in ventilation both with 5% carbon dioxide and with 100% oxygen than did the younger ones. In both age groups the effect of oxygen was to diminish the respiratory rate and that of carbon dioxide was to increase it.

The effects of various gas mixtures on infants whose minute volume had been diminished as a result of breathing 12% oxygen were also studied. In all the infants 5% carbon dioxide given along with 12% oxygen caused an increase in minute volume. This increase became more marked when 5% carbon dioxide with 20% oxygen was given, but the rate of increase was no greater than with 5% carbon dioxide and 12% oxygen; nor was the effect of a mixture of 5% carbon dioxide and 95% oxygen any greater than that of the mixture of 5% carbon dioxide and 20% oxygen.

Other observers have shown that in the foetus an increasing carbon dioxide tension in the foetal blood has little or no effect on respiratory activity, and that the important feat of initiating respiration at birth is achieved regardless of whether the carbon dioxide tension is low, normal, or high. The present investigations show that the respiratory activity of infants 2 to 24 hours after birth is profoundly influenced by an increase in carbon dioxide tension. From the practical point of view these results therefore support those who advise the administration of carbon dioxide in the treatment of asphyxia neonatorum, but the author feels that further investigations are necessary before an authoritative statement of the value of carbon dioxide therapy in neonatal asphyxia can be made. *R. M. Todd*

528. **Artificial Hibernation in Neonatal Pathology.** (L'hibernation artificielle en pathologie néo-natale)
M. LACOMME. *Semaine des hôpitaux de Paris* [*Sem. Hôp. Paris*] **30**, 3169–3172, Sept. 10–14, 1954.

After a discussion of the theoretical basis for the use of chlorpromazine in the treatment of neonatal disorders, the author describes his impressions of the treatment of ill premature infants, mature infants with birth injuries, and infants given exchange transfusions. The effect of chlorpromazine is to reduce body metabolism and oxygen requirements, thus lowering the body temperature; it is this last which has given rise to the term "artificial hibernation". It was given every 40 minutes by subcutaneous injection in doses totalling 1 to 1·5 mg. per kg. body weight per day. In 1952, 12 infants with neonatal shock were so treated, with 5 survivals; while of 30 premature infants of varying birth weights, 7 survived. From these initial experiences the author is convinced of the efficacy of this drug.

[None of the papers published in France on this subject known to the abstracter does more than give impressions of the clinical efficacy of the drug.] *David Morris*

529. **Preliminary Results of Hibernation Therapy in Infants at the Hôpital Saint-Vincent de Paul.** (Premiers résultats de l'hibernation chez le nourrisson à l'hôpital Saint-Vincent de Paul)
R. JOSEPH and F. ALISON. *Semaine des hôpitaux de Paris* [*Sem. Hôp. Paris*] **30**, 3173–3175, Sept. 10–14, 1954.

Experience at the Hôpital Saint-Vincent de Paul, Paris, of the use of what has come to be known as the "lytic cocktail", consisting of chlorpromazine, promethazine, and pethidine, in the treatment of neonatal disorders is reported in this brief paper. Among 17 infants under one year of age suffering from a variety of severe infections treated by this method there were 7 survivors. For inducing "artificial hibernation" chlorpromazine and promethazine are each given in doses of 1 mg. per kg. body weight in 1 to 3 hours by injection; the temperature soon falls, after which maintenance therapy is given, consisting of chlorpromazine and pethidine, 2 to 3 mg. per kg. per day, given either by intravenous infusion or intramuscularly at intervals of 3 to 4 hours for 36 to 48 hours. The efficacy of the drugs is ascribed to the hypothermia which enables the patient to withstand the effects of shock caused by the severe infection.

[As no clinical details are given and no mention made of comparison with the effects of other forms of treatment, it is impossible to evaluate with any accuracy the favourable claims made for this treatment.] *David Morris*

530. **Therapeutic Trial of 45 60 RP in Premature Infants.** (Essais thérapeutiques par le 45 60 R.P. chez le prématuré)
A. ROSSIER, J. MICHELIN, and I. HOLM. *Semaine des hôpitaux de Paris* [*Sem. Hôp. Paris*] **30**, 3182–3187, Sept. 10–14, 1954. 4 figs.

From the School of Puericulture in Paris comes this interesting report of observations on the use of chlorpromazine in the treatment of ill premature infants. The term "controlled hypothermia" is used in preference to the more commonly employed "artificial hibernation" of other French writers on the subject. The drug is given by mouth diluted with saline in hourly doses totalling 2 mg. per kg. body weight per day for 4 to 6 days. Where hyperexcitability or convulsions are present barbiturates are added. The temperature charts reproduced illustrate clearly the fall in body temperature and the influence of the temperature of the incubator in arriving at the desired level of body heat. The clinical indications for the use of the drug are given as respiratory difficulties, cyanosis, intense pallor, hypotonus or hypertonus, restlessness, convulsions, and "eye troubles"; favourable effects are reported on most of the symptoms. Of the 71 premature infants so treated, 26 survived. The authors state that it is too early and their experience too small for more than clinical impressions to be given, but that so far these are very favourable. *David Morris*

CLINICAL PAEDIATRICS

531. **Galactosaemia**
P. J. N. COX and R. J. P. PUGH. *British Medical Journal* [*Brit. med. J.*] **2**, 613–618, Sept. 11, 1954. 6 figs., 29 refs.

The authors describe 6 cases of galactosaemia in 3 families, and refer briefly to 25 previously reported cases.

The affected infants were normal at birth, but after the usual initial fall in weight they were rather slow to regain birth weight. Difficulty in feeding was accompanied by alternate bouts of lethargy and irritability and often by vomiting. During the first week the liver began to enlarge and this, in some cases, was associated with splenomegaly. Jaundice, usually of short duration, was

common, and the urine reduced Benedict's solution and usually contained albumin. The cerebrospinal fluid, when examined, contained large quantities of sugar, a finding which, in the authors' view, should suggest a diagnosis of galactosaemia. The only infant in the present series to survive developed cataract and was physically and mentally retarded. The authors found that mental retardation was a feature of many of the cases reported in the literature.

Treatment consists essentially in the exclusion of lactose and galactose from the diet. This is usually followed by an immediate and striking improvement, but of the 3 patients so treated in the present series, 2 had a relapse and died. *G. A. Smart*

532. **A Disease in Infants Resembling Chronic Wernicke's Encephalopathy**
I. FEIGIN and A. WOLF. *Journal of Pediatrics* [*J. Pediat.*] **45**, 243–263, Sept., 1954. 11 figs., bibliography.

A relatively uncommon disease process beginning in early infancy and characterized by failure to thrive, mental retardation, some spasticity or hypotonia of the limbs, ocular palsy, ataxia, muscular weakness, and occasionally involuntary movements is discussed and 3 fatal cases are described in detail. At necropsy the brain showed discoloured, somewhat softened areas of rarefaction with, on microscopical examination, an apparent, and possibly real, increase in the number of capillaries. Glial cells were not appreciably increased in number, and although many nerve cells in the affected areas had disappeared, others remained and appeared normal. There was marked deficiency of myelin. The lesions were situated chiefly near the walls of the third and fourth ventricles and the aqueduct, affecting the corpora quadrigemina; in some cases the substantia nigra, the corpus Luysi, the optic tract, and the dentate nucleus of the cerebellum were involved. One of the patients died at the age of one year; the other 2 patients, who were siblings, died at 21 months and 4 years respectively.

Some of the histological features in these cases resembled those of Wernicke's encephalopathy. There was no evidence of absolute or conditioned aneurin deficiency, and the authors suggest that a congenital metabolic disorder possibly involving the utilization of aneurin was present in these cases. *L. Crome*

533. **Clinical and Laboratory Differentiation between Herpangina and Infectious (Herpetic) Gingivostomatitis**
R. H. PARROTT, S. I. WOLF, J. NUDELMAN, E. NAIDEN, R. J. HUEBNER, E. C. RICE, and N. B. MCCULLOUGH. *Pediatrics* [*Pediatrics*] **14**, 122–129, Aug., 1954. 2 figs., 14 refs.

The differential diagnosis of herpangina from infectious gingivostomatitis is discussed. Clinically, the site of the lesions is the most important distinguishing feature, while bacteriologically, Group-A Coxsackie virus is isolated from cases of herpangina and the virus of herpes simplex from cases of gingivostomatitis. In herpangina, which is usually seen in the summer, there is sudden onset of fever, anorexia, sore throat, and dysphagia. Small grey-white, papulovesicular lesions with an erythematous base are found on the pharynx, tonsils, and soft palate. Symptoms persist for a few days only, and lesions for 4 to 6 days. At the Children's Hospital, Washington, D.C., 13 cases of herpangina were diagnosed clinically, and from 11 of these, 5 strains of Group-A Coxsackie virus were isolated by inoculation of saliva or faeces into suckling mice.

Acute infectious gingivostomatitis, which occurs throughout the year, is a more severe condition. The onset is gradual, with fever, dysphagia, sore mouth, and foetor oris. Hyperaemia, hypertrophy, and bleeding of the gums are present, and vesicles, which may later ulcerate, are seen on the gums, tongue, lips, and buccal mucosa. Cervical lymphadenopathy is common. The fever lasts 3 to 4 days, and the lesions persist for a fortnight. The virus of herpes simplex was isolated in 10 out of 12 cases in which acute infectious gingivostomatitis had been diagnosed on clinical grounds. Serum from 4 patients was tested for its power to neutralize herpes simplex virus, and a fivefold increase in titre was observed.

The authors found that other laboratory tests were of little value in the differential diagnosis of these two conditions. The bacterial and fungal flora present in the mouth of patients with herpangina was similar to that present in the mouth of patients with gingivostomatitis and was no different from that observed in healthy children. They emphasize the importance of good general management of patients with gingivostomatitis; in this series of cases administration of antibiotics was without effect. *A. Paton*

534. **Dental Structure and Caries in 5-year-old Children Attending L.C.C. Schools (1949 and 1951)**
M. MELLANBY and H. MELLANBY. *British Medical Journal* [*Brit. med. J.*] **2**, 944–948, Oct. 23, 1954. 4 figs., 7 refs.

The authors report the findings in the sixth of a series of surveys, begun in 1929, of the dental condition of 5-year-old London school-children. A total of 1,395 children from 26 schools were examined in 1951, established procedures and standards being used, and the findings are compared with those of the earlier surveys, particularly that carried out in 1949. There was an apparent set-back in 1949 in the dental improvement noted in the earlier surveys, there being fewer children without caries and an increase in the amount of hypoplasia and caries in individual teeth. The 1951 survey showed that 23·5% of the children were caries-free, compared with 24·9% in 1949, 37·5% in 1947) but only 4·7% in 1929), but that the surface structure of the teeth was better, 42·3% being free from hypoplasia as against 32% in 1949, the figures for the lower jaw being as usual substantially better than those for the upper.

A comparison is made of the incidence and extent of caries for all types of teeth in the five surveys since 1943, the incidence of caries being 30·1% in 1943, 26·5% in 1945, and 20·3% in 1947, rising again to 26·7% in 1949 and to 27·5% in 1951. The finding of a low incidence of caries in the lower incisors (2·6% to 3·8%) and of a

high incidence in the lower molars (54% to 65·1%) is in accord with experience.

The direct relationship between surface structure and caries was again demonstrated; thus in 1949 16·2% of the molars without hypoplasia and 65·8% with high degrees of hypoplasia were carious, the corresponding figures for 1951 being 30% and 75·2%.

F. T. H. Wood

535. **Primary Interstitial Pancreatitis in Infancy: an Anatomical and Clinical Study of Six Cases.** (Les pancréatites interstitielles primitives chez l'enfant. Étude anatomo-clinique de 6 observations)
C. NÉZELOF. *Archives françaises de pédiatrie* [*Arch. franç. Pédiat.*] **11**, 579–594, 1954. 8 figs., 26 refs.

From his experience at the Hospital for Sick Children, Great Ormond Street, London, and two children's hospitals in Paris, the author describes 6 cases of primary interstitial pancreatitis in infancy. On the basis of these and of 5 further cases reported in the literature he reviews the morbid anatomy of the disease. The clinical findings are rather indeterminate; on the other hand the histological appearances are quite distinct from that of fibrocystic disease of the pancreas or acute haemorrhagic pancreatitis.

The author considers that inflammatory or obstructive lesions of the ampulla of Vater are the most likely cause of this rare but interesting condition.

I. A. B. Cathie

536. **Hirschsprung's Disease as the Result of Maldevelopment of the Intramural Ganglia.** (Die Hirschsprungsche Krankheit als Folge einer Entwicklungsstörung der intramuralen Ganglien)
W. HÜTHER. *Beiträge zur pathologischen Anatomie und zur allgemeinen Pathologie* [*Beitr. path. Anat.*] **114**, 161–191, 1954. 15 figs., bibliography.

The absence of nerve cells from the intramural plexuses in the undilated rectosigmoid and their presence in normal numbers in the dilated colon in Hirschsprung's disease was first reported more than 30 years ago by dalla Valle, and although little attention was paid to this finding at the time, it has since been amply confirmed and has led to the introduction of recto-sigmoidectomy as the most effective treatment of this disorder. In a histological examination of 20 operation specimens and one necropsy specimen of the colon and rectum at the Bremen Pathological Institute, the present author found that not only were the nerve cells of the plexuses of Auerbach and of Meissner absent from a macroscopically normal segment of the rectosigmoid in all cases, but also the terminal reticulum of Stöhr, which he considers normally to consist of processes derived from the nerve cells, the abundant nerve fibres of this reticulum, which are mainly non-myelinated, being thus thought to be postganglionic sympathetic, and not preganglionic parasympathetic, fibres.

In view of the lack of any inflammatory or degenerative changes, the absence of nerve cells in the affected segment is generally attributed to a congenital agenesia, and for the further elucidation of this problem serial sections of human embryos were examined. Intramural ganglia were demonstrable in the primitive digestive tract at the foetal age of 7 to 8 weeks, differentiating in the cranio-caudal direction. In the rectum, however, the ganglia were recognizable at an earlier stage, possibly differentiating in the caudo-cranial direction. The author favours the immigration theory of the histogenesis of the plexuses as against the theory of autochthonous origin, and considers that the developmental error which results in Hirschsprung's disease takes place within the first 7 or 8 weeks of embryonic life.

H. S. Baar

537. **A Commentary on 120 Cases of Interstitial Pneumonia of the Premature Infant.** (Bericht über 120 Fälle von frühkindlicher interstitieller Pneumonie)
K. D. BACHMANN. *Zeitschrift für Kinderheilkunde* [*Z. Kinderheilk.*] **75**, 119–131, 1954. 6 figs., 24 refs.

The author describes the progress of a pneumonic infection attacking mainly premature infants which persisted from 1948 onwards at the University Children's Clinic, Cologne. This clinic, although it changed premises several times owing to war and post-war conditions, always retained its function as a unit. The infection did not seem to have been introduced into the clinic by any infant admitted and its origin in 1948 is obscure. However, in the course of the subsequent 5 years a diminishing number of premature infants were affected; in 1948, 3 out of 20 infants (15%) were involved, in 1949, 12 out of 111 (11%); in 1950, 14 out of 119 (12%); in 1951, 3 out of 138 (2·2%); but only one case occurred among 205 premature infants in 1952, and in 1953 the figure dropped to *nil*. The disease also occurred among full-term infants up to 4 months of age, the incidence in this age group increasing from 3 cases out of 765 (0·4%) in 1949 to 58 among 935 infants (6·2%) in 1953.

The incubation period was thought to be probably about 40 to 50 days, and there was possibly a seasonal variation in incidence, for although the number of cases was not sufficient to permit of any definite conclusion, it was noted that 43% of them arose in the months of May to July. The condition was never observed before the 6th week of life and the onset tended to be most common between the 11th and 14th weeks. The average mortality over the 5 years was 34·8%, but this figure varied considerably from year to year, being very high in March, 1953, while in the rest of that year the figure was far lower.

Treatment varied as new drugs became available, and has included the administration of aureomycin and chloramphenicol, and of the latter prophylactically, but the author feels that the most effective therapy was rest in bed in an oxygen tent. Prognosis was difficult; in most cases the fate of the infant seemed to be determined by the end of the first week. Among the children who died the duration of the illness ranged from 3 to 9 days (average 6 days); among those who survived the average length of illness was 14 ± 5 days. The condition seems now to have ceased to be a particular affliction of premature infants in this clinic, but the author emphasizes that it is a dangerous complication among newborn full-term infants.

J. G. Jamieson

Public Health

538. **Hospital Gastro-enteritis. An Epidemiological Survey of Infantile Diarrhoea and Vomiting Contracted in a Children's Hospital**
J. E. JAMESON, T. P. MANN, and N. J. ROTHFIELD. *Lancet* [*Lancet*] **2**, 459–465, Sept. 4, 1954. 3 figs., 15 refs.

A survey has been made of cases of endemic coliform diarrhoea occurring at the Royal Alexandra Hospital for Sick Children, Brighton, between 1947 and 1953. A bacteriological study covering the period 1950–3 revealed the presence of the specific O group 55 and O group 111 types of *Bacterium coli* as significant pathogens in the stools both of patients with gastro-enteritis and patients without symptoms. The latter are thought to be latent carriers of infection, which may also be spread by nurses and feeding bottles. On the basis of their experience of the epidemiology of hospital-acquired gastroenteritis in infants, the authors suggest measures to limit the spread of infection, including an isolation unit for admission of all suspected cases, long-term segregation of symptomless carriers, and the preparation of feeds by one nurse assigned to this duty.

D. Geraint James

539. ***Staphylococcus pyogenes* Cross-infection. Prevention by Treatment of Carriers**
J. C. GOULD and W. S. A. ALLAN. *Lancet* [*Lancet*] **2**, 988–989, Nov. 13, 1954. 3 figs., 8 refs.

540. **Immunization against Influenza.** (Zur Grippe-Schutzimpfung)
A. MANZ. *Zentralblatt für Arbeitsmedizin und Arbeitsschutz* [*Zbl. ArbMed. ArbSchutz*] **4**, 140–144, Sept., 1954. 1 fig., 9 refs.

A report is presented on an outbreak of influenza in two factories in Hamburg in 1953, during an epidemic which had its origin in south Germany and spread later to the north. In addition to routine precautions against transmission of infection in the two factories, 558 volunteers, constituting 12·5% of the workers, were inoculated with an adsorbed vaccine of influenza virus Type A 1, 173 receiving a subcutaneous injection of 0·4 ml. and the remainder 0·2 ml. Only 3·47% of the 173 workers who had been inoculated with 0·4 ml. of the vaccine developed clinical influenza compared with 5·71% of the 385 who had been given 0·2 ml. and 9·03% of those who had received no prophylactic treatment. The average duration of the illness was 6·35 days in the first group and 15 days in the other two.

Apart from headache and pain in the limbs on the first or second day after the inoculation, the general effects were slight. The local reactions were more serious, however, especially after the injection of 0·4 ml., with erythema, inflammation, and swelling at the site of the injection 24 or 36 hours later. Milder local reactions occurred after the injection of 0·2 ml. In view of these reactions the author recommends that an intradermal test be carried out before an immunizing dose of vaccine is given.

Franz Heimann

541. **Pathways of Influenza Spread**
A. ISAACS and I. ARCHETTI. *Lancet* [*Lancet*] **2**, 457–459, Sept. 4, 1954. 1 fig., 4 refs.

The world distribution, during a recent 4-year period, of strains of influenza virus A was studied at the National Institute for Medical Research, London. The strains of virus were isolated, maintained in fertile hens' eggs, and grouped antigenically from the results of agglutination-inhibition tests with ferret antisera.

Of 400 strains, 357 belonged to one or other of two distinct antigenic groups, the Liverpool or Scandinavian. A table shows that these strains were not distributed at random. In the countries of northern and central Europe the Scandinavian strains of virus predominated, and in southern Europe the Liverpool strains predominated. India and South Africa showed only the latter. It is stated that both varieties are capable of surviving up to 4 years in one country without significant antigenic variation. In some countries Scandinavian strains have taken the place of Liverpool strains, which are more closely related antigenically than the Scandinavian to the old A-prime variety. It is suggested that the immunity of a large proportion of the population in different countries may be remarkably uniform from the epidemiological point of view.

D. Geraint James

542. **Gamma Globulin in Epidemic Hepatitis. Comparative Value of Two Dosage Levels, Apparently Near the Minimal Effective Level**
M. E. DRAKE and C. MING. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **155**, 1302–1305, Aug. 7, 1954. 4 refs.

In a study of an epidemic of hepatitis in a closed institution, the observation that 0·01 ml. of gamma globulin per pound (0·5 kg.) of body weight protects against epidemic hepatitis with icterus was confirmed, and a dose of 0·005 ml. of gamma globulin per pound of body weight was found effective in preventing epidemic hepatitis with icterus. The 0·005 ml. dose was the less effective in the first 8 weeks, but apparently during this period it had permitted enough anicteric and inapparent infections to develop so that very few anicteric infections occurred after the eighth week, while many such infections continued to appear in those receiving the 0·01 ml. dose. The results of the study indicated that passive immunity afforded by gamma globulin lasts about two months or less, unless the treated person is continually exposed to infection during this period, and that passive-active immunization in epidemic hepatitis may occur on administration of gamma globulin.—[Authors' summary.]

Industrial Medicine

543. **Muscle Spasm in Manual Laborers**
A. HILTUNEN, M. J. KARVONEN, J. KIHLBERG, and R. LAMMINPÄÄ. *Archives of Industrial Hygiene and Occupational Medicine* [*Arch. industr. Hyg.*] **9**, 476–480, June, 1954. 8 refs.

The incidence and anatomical distribution of hard and painful muscles in 430 men doing manual work were investigated at the Institute of Occupational Health, Helsinki. The presence of hard and painful muscles was determined by palpation. [For a statistical analysis of the findings the original paper should be consulted.]

Studying the incidence of myalgia in various occupations the authors found that the number of affected muscles increased significantly as the occupation called for more physical work; the incidence of myalgia was not, however, related to age. The muscles most commonly affected were those doing static work—for example, the calf muscles. It is emphasized that muscular work is not the only causative factor, mental as well as general and environmental factors playing a part.

The condition is regarded as trivial in most cases, many workers being unaware of it before examination; but there are others who suffer considerable annoyance and inconvenience from this form of myalgia. Preventive measures include better planning of working methods, avoidance of excessive standing at work, and exercises in " active relaxation ". *R. E. Lane*

544. **Trichloroethylene and Dichloroethylene Poisoning**
R. S. MCBIRNEY. *Archives of Industrial Hygiene and Occupational Medicine* [*Arch. industr. Hyg.*] **10**, 130–133, Aug., 1954.

Trichloroethylene is one of the chlorinated hydrocarbons most widely used in industry as a solvent for fat and grease, being non-corrosive and non-inflammable and, in normal circumstances, free from toxic effects. Dichloroethylene is used for similar purposes, though not so widely. To illustrate the results of continued exposure to high concentrations of trichloroethylene and dichloroethylene, a number of case histories are reported. In the first case exposure to air " well saturated " with the vapour of trichloroethylene caused burning of the face—a brilliant erythema—and of the hands, which were also slightly blistered, having come in contact with the liquid solvent. Another group of cases of trichloroethylene poisoning occurred among women employed in cleaning optical lenses by means of cotton wool held between finger and thumb and dipped in trichloroethylene. After " a few months " about half the workers suffered paralysis of the thumb and forefinger of the hand so used, with loss of tactile sense, the disability continuing for several months. There was no skin damage.

A mixture of trichloroethylene (40%) and dichloroethylene (60%) used in a heated degreasing tank caused poisoning in the operator whose task was to immerse the articles, contained in a wire basket, in the tank for a few seconds, lift them out, and put them upon the floor to dry; the solvent dripped from the wet baskets on to his feet, while his hands were protected from heat by cotton gloves which were usually damp with the solvent. After an unstated period [but more than a few weeks] this man collapsed at work and was detained in hospital for a few days complaining of dizziness. A month later he was readmitted to hospital complaining of numbness and pain in his fingers and feet, double vision, hoarseness, loss of weight, pains and tenderness in the muscles of his legs, inability to walk properly or to use his hands to grasp and hold, and impotence. His hands were claw-like, hot, and painful, with loss of sensation; sensation was lost also in both feet, which were flexed and painful. The diplopia continued for 6 weeks, aphonia for one week, and impotence for two months. There was atrophy of the interossei and of the muscles of the thenar and hypothenar eminences of both hands. Recovery was complete after one year. Aneurin was found to be of value in treatment. Finally, the fatal case is reported of a worker employed in the extraction of oil from fish livers by means of dichloroethylene and who had suffered excessive exposure to high concentrations of the vapour. Death was due to bronchopneumonia, most of the organs showing oedema and congestion.
M. A. Dobbin Crawford

545. **Trichloroethylene Toxicity. Report of Five Fatal Cases**
M. KLEINFELD and I. R. TABERSHAW. *Archives of Industrial Hygiene and Occupational Medicine* [*Arch. industr. Hyg.*] **10**, 134–141, Aug., 1954. 33 refs.

Having noted that reports in the literature of the toxic effects of trichloroethylene are predominantly of European origin and that no deaths have been officially reported from this cause in the U.S.A., the authors instituted a search of the records of the New York State Department of Labor and discovered reports of 5 deaths which they now believe to have been due to trichloroethylene. Four of the men concerned had been employed in degreasing operations and were exposed to high concentrations of trichloroethylene. All had complained of symptoms such as drowsiness, nausea, dizziness, and vomiting, yet had continued at work. All died suddenly, one while at work, and the others each a few hours after work. The necropsy findings in all were very similar, trichloroethylene being present in the organs in varying quantities, with some congestion of the viscera but no gross pathological changes. It is thought that the immediate cause of death was ventricular fibrillation. The fifth man was poisoned by accidental ingestion of trichloroethylene. He died 11 days later, the cause of death being a marked lower nephron

nephrosis together with severe centrilobular necrosis of the liver and acute pancreatitis.

There is some difficulty in defining the acute toxicity of trichloroethylene and opinions are divided as to the effects of continued exposure. The cumulative effects have not been determined. On account of this lack of definition, the medico-legal implications present a difficult problem. In the control of the trichloroethylene hazard, determination of the amount of trichloracetic acid excreted by the kidneys should be more widely practised, for there seems to be a fair correlation between the quantity so excreted and the concentration of trichloroethylene in the air breathed. It is urged that the maximum allowable atmospheric concentration should not be increased above the present figure of 100 p.p.m.

M. A. Dobbin Crawford

546. **Acute and Subacute Toxicity of Cyclethrin**

C. P. CARPENTER, C. S. WEIL, U. C. POZZANI, and H. F. SMYTH. *Archives of Industrial Hygiene and Occupational Medicine* [*Arch. industr. Hyg.*] **10**, 162–168, Aug., 1954. 4 refs.

The toxicity of the insecticide "cyclethrin" is similar in effect to that of allethrin (of which it is the *cyclo*pentenyl analogue) and the pyrethrins and no greater in degree. A single application of 0·01 ml. of undiluted cyclethrin to the shaved skin of rabbits produced a minimal response in one of 5 rabbits used. Eight intracutaneous injections, given at intervals of 2 or 3 days, of a 0·1% dispersion of cyclethrin in propylene glycol and saline were followed 21 days later by a challenge dose, but there was no evidence of sensitization. To determine the results of inhalation, rats were exposed to a dense fog of 86·4% cyclethrin in which the diameter of most of the droplets was less than 2 μ and whose cyclethrin content was 19·1 mg. per litre. Of 10 rats exposed for 4 hours, 3 died. This concentration is 10,000 times the usual effective concentration for the aerosol disinfestation of aircraft, and 30,000 times the concentration for household use. Rats exposed to lower concentrations all survived.

The effects of repeated inhalation were determined by exposing dogs and rats on 42 occasions (twice daily, 5 days a week) for 30 minutes to an aerosol containing 1% cyclethrin in peanut oil and freon. This is 10 times the anticipated effective concentration for freeing aircraft of insects, and 30 times that for household use. No significant injury resulted in any of these animals.

M. A. Dobbin Crawford

547. **Occupational Disease due to Acetone: Clinical Features, Field Investigations, and Physiopathological Researches.** (Patologia professionale da acetone: manifestazioni cliniche, indagini negli ambienti di lavoro e ricerche fisiopatologiche)

L. PARMEGGIANI and C. SASSI. *Medicina del lavoro* [*Med. d. Lavoro*] **45**, 431–468, Aug.–Sept., 1954. 11 figs., bibliography.

This paper from the Industrial Medical Clinic of the University of Milan is in three parts, of which the first records investigations carried out at three factories using acetone, in which an atmospheric concentration of acetone ranging from 0·029 mg. to 2·18 mg. per litre was found. The highest of these concentrations is approximately equal to the present recommended maximum permissible concentration (1,000 p.p.m.). Clinical examination of 22 employees who were exposed to the highest concentrations of acetone showed a high incidence of chronic conjunctivitis, pharyngitis, bronchitis, and gastritis. Acute intoxication by acetone is rare; the authors report 5 cases, all of which occurred in exceptional circumstances during the stabilization of a process for the production of cellulose acetate. The main features were narcosis and mucosal irritation.

Part II describes laboratory investigations undertaken in order to study the absorption, elimination, and behaviour of acetone in the body in conditions comparable with those of occupational exposure. It was shown that acetone is eliminated through the human skin up to an amount equal to one-quarter of that eliminated in the expired air. Acetone is also excreted in the saliva, and was found in the duodenal juice following intravenous injection. It could not be found in significant amounts in the faeces. The absorption of acetone through the intact skin was demonstrated experimentally.

In a study of the metabolism of acetone the respiratory quotient 2 hours after the administration of an oral dose of 80 mg. of acetone per kg. body weight to a single subject was found to have fallen from 0·905 to 0·710. The extent of this fall suggested a closer examination of the quantitative metabolic changes due to the absorption of acetone in the light of present knowledge of the interconvertibility of ketone bodies, from which it was shown that with a respiratory quotient of 0·710 three-fifths of the respiratory exchange is accounted for by normal metabolic processes, the remaining two-fifths being due to destruction of ketone bodies. This complex situation is fully discussed. When subjects doing light work and with normal diuresis were given a dose of 5,000 to 5,800 mg. of acetone approximately 220 to 350 mg. was eliminated in the expired air, 80 to 150 mg. in the urine, and 50 mg. through the skin, but the variations were very wide. Only 8% of the dose was eliminated in the first 24 hours, the remaining 92% being metabolized; this finding differs considerably from those published by various American authors and the reasons for this are analysed in detail. Marked individual variations in blood acetone level were found between the 6th and 12th hours following an oral dose and it was concluded that the metabolism of exogenous acetone in active subjects cannot be exactly determined.

In Part III the practical application of the experimental results in industrial medicine is discussed. It is recommended that the maximum permissible concentration of acetone should again be reduced to 500 p.p.m. and it is pointed out that in assessing it as an occupational hazard more reliable information is obtainable from the determination of acetone concentration in the blood, expired air, or urine than from the measurement of atmospheric concentration. A study of the acid–base balance in workers exposed to acetone is also recommended and brief notes on the prevention and treatment of acetone poisoning are appended. *L. G. Norman*

Forensic Medicine and Toxicology

548. **Applications of Antiglobulin Reaction to Bloodstains in Determination of Animal Species**
J. R. ANDERSON. *American Journal of Clinical Pathology* [*Amer. J. clin. Path.*] **24**, 920–928, Aug., 1954. 11 refs.

In 1949 it was shown by Wiener *et al.* (*Proc. Soc. exp. Biol.* (*N.Y.*), 1949, **71**, 96) that treatment with high dilutions of human serum annulled the capacity of an anti-human-globulin serum to agglutinate human erythrocytes coated with incomplete isoantibody, whereas the serum of several other species, including the monkey *Macaca mulatta*, possessed very little or no such inhibitory property. Antisera, however, vary in specificity and there was no evidence that inhibition of the antiglobulin reaction would prove a more specific test for identifying human blood in blood stains than the direct precipitin test now in general use. In studies carried out at the Western Infirmary, Glasgow, the author set out to investigate if this were so or not.

The antisera used were developed by immunizing rabbits against human serum. Before use, agglutinins were removed by absorption on erythrocytes from human Group-O, Rh-positive blood. The antiglobulin property of the antisera was determined by demonstrating their capacity to agglutinate erythrocytes coated with incomplete antibody. Two techniques of the practical application of the proposed test to the examination of dried blood stains on cloth are described in this paper, and the uniformity of the results is demonstrated. The author claims to have established that such tests are more highly specific than the direct precipitin test in general use. *Gilbert Forbes*

549. **The Danger of Accidental Carbon Monoxide Poisoning. A Review of 100 Cases**
K. SIMPSON. *British Medical Journal* [*Brit. med. J.*] **2**, 774–776, Oct. 2, 1954. 1 ref.

There are some 400 to 500 cases of accidental poisoning from domestic coal-gas in England and Wales every year, and in this paper from Guy's Hospital (University of London) the author reviews 100 consecutive fatal cases, the object being to draw attention to: (*a*) common dangers inherent in present usage of coal-gas in the home; (*b*) other, unsuspected, sources of carbon monoxide pollution of the air; and (*c*) the urgent need for adequate warning of danger and for safety devices in domestic apparatus. The number of fatal cases was more or less the same at all ages until about the age of 60 years, after which there was a sharp rise to about four times the number at any earlier age period; in fact 66 of the 100 victims were over 60 years of age. This rise is attributed to increasing age and forgetfulness, senile decrepitude, or frank collapse. The main causes of these accidents in order of frequency were: (*a*) trivial accidents with taps or burners and partly turned stop cocks; (*b*) ignorance of the danger of inadequate ventilation and blocked flues; (*c*) leaking apparatus and faulty mains; and (*d*) exposure to gas as a result of collapse due to natural disease or other causes such as drunkenness. Examples of fatal cases are cited. The author emphasizes the danger of the common meter and the grave risk of burning gas, whatever the appliance used, in premises where there is insufficient ventilation. He claims that 70 to 75 of these 100 fatal cases could reasonably have been prevented, and considers that steps should be taken to deal with the problem, which is not insuperable. *Gilbert Forbes*

550. **Poisoning by Barbiturates**
P. R. V. D. R. COPEMAN. *Journal of Forensic Medicine* [*J. Foren. Med.*] **1**, 271–283, July–Sept., 1954. 6 refs.

The author reports that in recent years the number of deaths from barbiturate poisoning in South Africa has risen alarmingly, 112 such cases having been investigated at the Government Chemical Laboratory, Johannesburg, during the period 1948–52, as compared with 115 deaths from arsenical poisoning. Of the persons dying of barbiturate intoxication, only 4 were non-European, and 74 were regarded as having committed suicide. The concentrations of barbiturates found in the organs are recorded, and the methods of investigation are described. The most useful method for the general detection of the presence of barbiturate was found to be the cobalt nitrate test, but individual compounds were best identified by determination of the melting point of the fully purified residue, although this is not always possible owing to the very small amount available.

From analysis of his results the author concludes that the concentration of barbiturate in the liver may be used as a criterion of the amount absorbed by the system in general, and that the distribution of the drug in the organs is not uniform, depending largely on individual constitution. The importance of urine analysis in diagnosis, particularly while the subject remains alive, is emphasized. Analytical data were not found to be of value in distinguishing between cases of suicide and of death due to accidental overdosage, nor did they permit any conclusions to be drawn on the effect of barbiturates taken in conjunction with alcohol or a second hypnotic. Barbitone ("veronal") and phenobarbitone ("luminal") were considered to be less toxic than the other compounds studied, judging from the amounts found in the liver and kidneys. The author's findings regarding the persistence of barbiturate in the body are presented, and the importance in treatment of rapid elimination is emphasized, with special reference to emptying of the stomach, in which a significant amount of the drug may remain unabsorbed for a considerable time.
P. N. Magee

Radiology

RADIOTHERAPY

551. **Changes in the Phagocytic Activity of Polymorphonuclear Leukocytes following Total Body *X*-irradiation in the Rat**
M. WILKINSON. *Blood* [*Blood*] **9**, 810–816, Aug., 1954. 1 fig., 8 refs.

The phagocytic activity of polymorphonuclear leukocytes from irradiated rats was studied over a period of 13 days following 550 r total body *x*-irradiation. Leukocytes from irradiated rats showed slightly increased phagocytosis of plague bacilli during the first 6 days after irradiation, but on statistical analysis this increase proved to be insignificant. From the seventh to the thirteenth day after irradiation, these cells showed a markedly reduced capacity to phagocytose plague bacilli.

Phagocytic studies on suspensions of normal cells in plasma from irradiated animals and on cells from irradiated animals in normal plasma showed that the deficient phagocytosis during the second week following irradiation was due mainly to a defect in the polymorphonuclear leukocytes themselves, though the fact that the addition of normal plasma to cells from irradiated animals did increase their phagocytic capacity by a small but definite degree suggests that there is also a defect in the plasma of irradiated animals.—[Author's summary.]

552. **Roentgen-ray Therapy of Cerebral Metastases**
JEN-HUNG CHAO, R. PHILLIPS, and J. J. NICKSON. *Cancer* [*Cancer* (*N.Y.*)] **7**, 682–689, July, 1954. 1 fig., 20 refs.

From their experience at the Memorial Center for Cancer and Allied Diseases, New York, the authors assess the palliative value of treating metastatic intracranial tumours by irradiation. They point out that although the successful removal from the brain of a soiltary metastasis has occasionally been reported, the tumours are usually multiple and therefore suitable only for palliative treatment. The symptoms are often extremely distressing both to the patient and the relatives, and are also such as to increase the difficulties of nursing the patient. *X*-ray therapy, to a dose of about 3,000 r, may relieve these symptoms for a few months, which is often all that is necessary because of the rapid progress of the primary malignant disease elsewhere in the body towards a fatal termination.

The results in 38 cases are reported. A good degree of palliation of symptoms resulted in 24 cases, and of the 14 failures, 9 were attributed to insufficient dosage. A dose to the whole brain of about 3,000 to 4,000 r in 3 or 4 weeks is aimed at, and for this purpose *x* rays at 250 kV (H.V.L. 2 mm. Cu) are usually sufficient. (In exceptional cases in which improvement is unduly slow, the patient may be transferred to supervoltage therapy.) In the authors' usual method two opposed lateral fields are used, the lower margin of the field running along the supraorbital ridge and back through the external auditory meatus and so across the line of the foramen magnum. The fields overlap the frontal, vertical, and occipital regions of the head on to bolus bags. Daily treatment is begun cautiously with 50 to 100 r, and if there are no untoward symptoms the dose is gradually increased to 400 r daily.

The authors feel that such palliative treatment is worth while in all cases of intracranial metastases, irrespective of the nature of the tumour, when the expectation of life is more than a very few weeks. In 14 of the 24 cases which responded to treatment the average period of survival was 8·2 months, while in 12 of the 14 which did not respond it was only 4·6 months.

E. Stanley Lee

553. **A New Method of Direct Irradiation of the Larynx. Some Remarks on the Radiotherapy of Cancer of the Larynx.** (Présentation d'une nouvelle méthode d'irradiation directe du larynx. Quelques réflexions à propos de la radiothérapie des cancers du larynx)
P. LAMARQUE and A. ROMIEU. *Bulletin de l'Association française pour l'étude du cancer* [*Bull. Ass. franç. Cancer*] **41**, 223–234, 1954. 9 figs., 1 ref.

The radiotherapy of cancer of the larynx is usually carried out by external irradiation, the whole tumour bed thus receiving as large a dose as the primary growth. This is undesirable and may be responsible for many of the failures, whereas if it could be avoided the results should be as good as in cancer of the skin. The authors have previously developed a special apparatus for the intracavitary treatment of lesions in such sites as the rectal ampulla, mouth, and pharynx, using 100 kV with a tungsten target at 45 degrees and a lateral beryllium window. A pipe-shaped "localizator" with an endoscopic lighting system for visualization through the bowl is first inserted, after which the *x*-ray tube is introduced through the stem. Doses of 500 r can be given in a few seconds with 1 mm. aluminium filtration, and total doses of 7,000 to 8,000 r used. This method is comparable to that of Chaoul, and the results have been very encouraging.

For treatment of the larynx, however, the epiglottis prevents the use of this apparatus and a new method has therefore been devised, using direct laryngoscopy under local anaesthesia. The *x*-ray tube is introduced at right-angles to the endoscopic tube, and irradiation carried out at 10 cm. distance with an output of 360 r per minute. Three doses of 500 r are given per week, to a total of 6,000 to 10,000 r in 4 weeks. Lesions of the ventricular bands, arytenoids, and pyriform fossa have been treated, with a good response. In case of failure, surgery of the primary tumour or lymph nodes

is still possible, without any embarrassment from post-radiation effects. So far only inoperable cases have been treated, but the early results are encouraging and a wider trial appears justified. *J. Walter*

RADIODIAGNOSIS

554. **Comparison between Encephalography and Ventriculography.** [In English]
M. DAVID, G. RUGGIERO, and J. TALAIRACH. *Acta radiologica* [*Acta radiol. (Stockh.)*] **42**, 37–42, July, 1954. 1 fig., 4 refs.

It is commonly held that encephalography is contra-indicated in cases of brain tumour, particularly in the presence of raised intracranial pressure. At Saint Anne's Hospital, Paris, the authors carried out encephalography in 40 cases of brain tumours and in this paper they compare the results with those obtained by ventriculography in 23 cases. Both groups included patients with a tumour in the posterior fossa and with severe papilloedema. Encephalography was carried out according to the technique of Lindgren. Not more than 25 to 30 ml. of air was injected before cerebrospinal fluid was withdrawn, and the volume of fluid withdrawn was always less than the quantity of air injected. These precautions are considered to reduce considerably the risk of cerebral or cerebellar herniation.

The untoward sequelae which occurred in both groups are described. After encephalography 3 patients had temporary loss of consciousness, but the tumours were subsequently removed successfully. A further patient with cerebellar herniation was considered to be too ill for operation and died. Of the patients subjected to ventriculography, 4 became comatose and although operation was performed at once, 3 died; the fourth patient recovered after the tumour was removed. The authors conclude that encephalography is not more dangerous than ventriculography and has the very real advantage that it permits preoperative diagnosis of cerebellar herniation; moreover, the brain appeared to be much less congested after encephalography than after ventriculography. *G. Ansell*

555. **Cerebral Thrombosis in the Carotid or Vertebral Angiogram.** (Gefässverschlüsse im Carotis- und Vertebralisangiogramm)
K. DECKER and E. HOLZER. *Fortschritte auf dem Gebiete der Röntgenstrahlen* [*Fortschr. Röntgenstr.*] **80**, 565–575, May, 1954. 5 figs., 34 refs.

The authors give an account of their method of carrying out vertebral and carotid angiography on patients suffering from cerebral vascular occlusion, a procedure which is generally considered dangerous. In preparation, a subcutaneous injection of the antihistaminic " synopen " with atropine is given, with the result that hardly any allergic reactions occurred in their 97 patients. The contrast agent used is " per-abrodil M " 45%. A thin needle with an external diameter of 1 mm. is recommended as the tip should lie freely in the vessel lumen, and 8 ml. is administered at each injection, 25 ml. being the upper limit for the complete examination. The interval between injections should be at least 10 minutes. Three or 4 exposures are made within 3 to 5 seconds, with the patient's head lying laterally. To avoid false diagnoses it is necessary to show the tip of the needle in each radiograph.

The site of the occlusion in the authors' cases was as follows: carotid artery—cervical portion, 35 cases; carotid artery—intracranial portion, 7; middle cerebral artery, 42; anterior cerebral artery, 2; posterior cerebral artery, 1; vertebral artery—basal portion, 3; ophthalmic artery, 1; and multiple occlusions, 6.

The cause of the occlusion was an endarteritis in 26 cases, arteriosclerosis in 12, syphilis in 11, embolus in 14, and other or unidentified causes in 34 cases. In a number of cases thromboses in the wall of the carotid artery were observed, and these were regarded as a potential source of future cerebral emboli in those cases in which the heart did not show any organic change.

The authors describe one case of recanalization of a previously occluded vessel after conservative treatment with heparin. Six months after the cerebral lesion occurred the angiogram appeared to be completely normal, although the patient's paralysis and aphasia persisted unchanged.

They also observed circulatory slowing in the region of the damaged vessels, which they regard as the cause of hypoxaemia which in turn leads to changes in the brain tissue not amounting, however, to necrosis.

It is not possible radiologically to outline small arteries such as the choroidal artery sufficiently well to obtain any satisfactory detail of diagnostic value.
J. Rabinowitch

556. **Bronchography under Brief Anaesthesia with Thiopentone and " Lysthenon " (Succinylcholine Chloride).** (Die Röntgenbronchographie in Pentothal-Lysthenon-(Succinylcholinchlorid-)Kurznarkose)
A. LEB. *Fortschritte auf dem Gebiete der Röntgenstrahlen* [*Fortschr. Röntgenstr.*] **81**, 119–126, Aug., 1954. 4 figs., 28 refs.

The method of bronchography described by the author has been developed at the Central Röntgen Institute, Graz, to obviate two existing difficulties associated with present bronchographic techniques, namely, the danger of inadequate local anaesthesia, and the rather slow absorption of the viscous vehicle (carboxymethyl cellulose) used with water-soluble contrast agents. During the past three years he has performed over 400 bronchographies after injection of " lysthenon " (succinylcholine chloride), a muscle relaxant with a rapid but very short-lasting action which has no effect on the circulation and is well tolerated. It is superior to tubocurarine because of its brief effect and the fact that it does not require the administration of an antidote after its use.

The detailed procedure is described as follows. As premedication, an intramuscular injection of 50 mg. of " largactil " (chlorpromazine hydrochloride) is given one hour before the examination to reduce oxygen consumption, along with 50 mg. of " phenergan " (promethazine

hydrochloride) as an antihistaminic, followed 30 minutes later by atropine and a codeine preparation to reduce secretion and to restrict coughing. For the examination itself the patient is placed on a tilting *x*-ray table (which should be motor-driven) and 0·5 g. thiopentone injected intravenously, followed by 50 mg. of lysthenon as soon as the patient is asleep. Intratracheal intubation is then carried out as quickly as possible, as the respiratory musculature is paralysed. A tracheal tube with a lumen 7 mm. in diameter is used, this permitting the entry of a Metra's catheter and yet leaving room for the simultaneous administration of oxygen. It is important that the catheter should be freely movable inside the tube and that its position can be altered very quickly. As soon as the tube is in position oxygen is introduced under pressure to make up for the period of respiratory paralysis.

The bronchographic examination is carried out under screening control. The position of the catheter can be clearly seen below the tracheal tube, which should not be introduced farther than to a point 1 or 2 cm. above the bifurcation; by turning the catheter it is possible to direct it into the desired lobe. The dye is injected into the affected lobe and a localized view of this area taken. The patient is then rotated and tilted into such a position that a clear view of all the branches of the bronchus being examined is obtained and further films are exposed. After additional injections of contrast medium serial radiographs of the differentially filled bronchial tree may be obtained. As soon as bronchography is completed a powerful suction apparatus is attached to the catheter and in a few seconds the major portion of the contrast medium is sucked out of the bronchial tree. It is essential that throughout the administration of the medium and during the process of suction no oxygen be administered under pressure, otherwise the dye will be driven into the alveoli. If a water-soluble medium is used it can be aspirated very easily. The total time of the examination should not exceed 5 or 6 minutes, the time during which the patient receives no oxygen being about 2 minutes; this procedure has been well tolerated by all patients. The advantages of the method are that it ensures a much more complete filling of the individual bronchi, with exact localization in all directions, and that the bronchial muscular relaxation allows the whole lumen of the bronchus to be outlined by the dye, thus disclosing early changes which might otherwise be missed. There is no mental trauma associated with this technique and dangerous local anaesthesia is avoided.

J. Rabinowitch

557. **An Anatomical Explanation of the Formation of Butterfly Shadows**

G. HERRNHEISER and K. F. W. HINSON. *Thorax* [*Thorax*] 9, 198–210, Sept., 1954. 17 figs., 32 refs.

In this paper from the London Chest Hospital the authors first describe fully the radiological features of "butterfly" or "batswing" shadows in the lungs, and then give a summary of the few pathological reports on the condition found in the literature; the essential lesion is almost certainly an oedema of the central parts of the lungs. Among the various aetiological factors which have been cited are uraemia and renal azotaemia, left-sided cardiac failure, and neurogenic disorders. On the basis of a detailed study of the anatomy of the lung (in which the concept of a cortical and medullary zone is emphasized) and of the anatomy of the pulmonary blood supply, the authors consider that variations in the distribution of the vessels in the two zones, together with the variation in function of the zones, would account for the distribution of the butterfly opacities. They refer to Kerley's suggestion of the possibility of the formation of shunts similar to those which have been described in the kidney. (In an addendum to their paper the authors call attention to the recent study by Prichard *et al.* (*Brit. J. Radiol.*, 1954, **27**, 93) in which the observations here reported in man were confirmed experimentally in animals by means of angiographic studies.)

Sydney J. Hinds

558. **The Roentgenographic Image of the Azygos Vein: a Possible Source of Diagnostic Confusion**

F. H. ELLIS and A. BRUWER. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **29**, 508–513, Sept. 1, 1954. 2 figs., 15 refs.

In routine radiographs of the chest the shadow of the azygos vein may occasionally be mistaken for a mediastinal tumour or enlarged paratracheal lymph nodes, the true source of the shadow being recognized only in the course of subsequent exploratory thoracotomy. Familiarity with the radiographic appearances of the azygos vein is therefore important.

In the routine postero-anterior projection of the chest the shadow of the azygos vein lies along the right wall of the trachea in the region of the upper-lobe bronchus. It is usually oval or spindle-shaped, the lower pole being larger than the upper. It may vary in size and shape from a flat inconspicuous shadow to a prominent, well-defined density. Tomography is of great value for the accurate definition of the typical outline of the azygos vein. Fluoroscopy may add further information in doubtful cases. During the performance of the Valsalva manœuvre or other procedures which increase the intrathoracic pressure the shadow cast by the azygos vein may be seen to fluctuate in size.

A. Orley

559. **Supervoltage and Multiple Simultaneous Roentgenography—New Technics for Roentgen Examination of the Chest**

W. J. TUDDENHAM, J. F. GIBBONS, J. HALE, and E. P. PENDERGRASS. *Radiology* [*Radiology*] **63**, 184–191, Aug., 1954. 7 figs., 8 refs.

There can be few radiologists who have not at one time or another missed the signs of atelectasis in a left lower lobe on a conventional postero-anterior chest radiograph, the usual radiological technique employed producing good detail in the lung fields with underexposure of the mediastinum, while penetrated films show mediastinal detail but result in overexposure of the lungs. As a possible solution of this difficulty the authors have experimented with a 2,000,000-volt *x*-ray generator in an attempt to produce low-contrast films

showing detail in both the lungs and mediastinum. The factors employed were 2,000 kV, 100 μA, and exposure at 3 seconds at 56 in. (1·4 m.) anode–film distance. The special films used were exposed between lead–antimony intensifying screens 0·005 in. (0·127 mm.) thick. The exposure time had to be high because of the relative insensitivity of film to such very short wavelengths.

From the results of a limited clinical trial carried out at Massachusetts General Hospital, Boston, the authors report that the films obtained were considerably " softer " than conventional chest radiographs. Mediastinal structures, particularly the larynx, trachea, and bronchi, were well seen in addition to the lungs. Emphysematous bullae and air-filled cavities in the lung were also demonstrated more clearly. Unfortunately, however, the long exposure time results in some blurring of detail.

[The authors do not mention a very much simpler and cheaper method of producing the type of radiograph they illustrate and describe. If postero-anterior chest films are overexposed by 25 to 50%, and then developed for only 50 to 75% of the normal developing time, good low-contrast films result, with detail in both the lungs and mediastinum.] *D. E. Fletcher*

560. **Myelography to Help Localize Traction Lesions of the Brachial Plexus**
I. M. TARLOV. *American Journal of Surgery* [*Amer. J. Surg.*] **88**, 266–271, Aug., 1954. 3 figs., 5 refs.

It is generally agreed that traumatic lesions of peripheral nerves, including the brachial plexus, should be explored as soon as safely possible. This principle is equally applicable to trauma of the nerve roots. Difficulty may be experienced, however, in determining whether the lesions are intraspinal or extraspinal, although help may be obtained clinically by noting the presence or absence of Horner's syndrome and the function of the rhomboid and serratus anterior muscles in lesions of the brachial plexus.

The author, writing from the New York Medical College, New York, claims that myelography is helpful in differentiating these lesions, and describes two specific appearances: (1) replacement of the normal axillary pouchings of the nerve roots by medially concave defects on the affected side; and (2) an extrameningeal cavity communicating with the subarachnoid space. These findings were confirmed at operation, and details of 3 cases are given. *W. B. D. Maile*

561. **Pneumomediastinography by the Retroxiphoidal Route.** (Le pneumomédiastin par voie rétroxiphoïdienne)
A. BALMES and A. THEVENET. *Poumon* [*Poumon*] **10**, 385–393, May, 1954. 6 figs.

The authors recommend the method of pneumomediastinography by the retroxiphoidal route since it is simple to perform, requires no special apparatus, is perfectly harmless, gives good contrast, and may supply valuable information. Their technique is as follows. The tip of the xiphoid process is located by palpation and a local analgesic is injected about 1 cm. above this point in the middle line. A small lumbar-puncture needle is pushed obliquely through the tissues of the linea alba, tilted towards the abdomen, and made to penetrate to a depth of about 2 cm. along the posterior surface of the xiphoid process. The stylet of the needle is then withdrawn, a preliminary injection of about 20 ml. of air is made into the tissues, and if there is no air-reflux (indicating that the needle is well in the right space) the needle is then connected to the tube of a Küss apparatus and 500 to 600 ml. of air injected under a pressure of about 5 to 10 cm. of water.

The distribution and spread of the injected air is followed at half-hourly intervals on the *x*-ray screen and radiographs may also be taken at this juncture. During this time the patient is placed with the head well up in order to facilitate the passage of the air into the posterior mediastinum. When the air has spread as far as it can go, frontal and sagittal tomograms are taken. In some cases a barium swallow may supply additional information regarding the oesophagus. By this method it is possible to determine whether an observed opacity has its origin in the thoracic wall, the pleura, the parenchyma, or the mediastinum. *A. Orley*

562. **Accessory Vessels of the Kidney and their Diagnosis in Hydronephrosis.** [In English]
G. EDSMAN. *Acta radiologica* [*Acta radiol.* (*Stockh.*)] **42**, 26–32, July, 1954. 5 figs., 16 refs.

Accessory vessels to the upper or lower poles of the kidneys may arise as supernumerary branches from the aorta, as abnormal branches of the renal arteries, or from the iliac arteries. At Sahlgrenska Sjukhuset, Gothenburg, the vascular supply of the kidney was studied by aortography in 200 patients (388 kidneys). Accessory vessels to the lower pole were found in 63 kidneys, and in 20 (31·7%) of these there was an associated hydronephrosis. In the other 325 kidneys the incidence of hydronephrosis was only 7·1%. In order to assess the importance of an individual artery in the causation of hydronephrosis, the author recommends that the renal pelvis should first be filled with contrast medium by excretion urography, after which aortography should be performed with the patient in the prone position. In this position the uretero-pelvic junction of a hydronephrotic kidney is at the lowest point of the renal pelvis, and is liable to be pressed on by a stretched aberrant vessel passing ventrally. The relationship of the artery to the renal pelvis can then be clearly demonstrated, and on the subsequent radiograph it is possible to assess the thickness of parenchyma surrounding the renal pelvis.

The arteries of the kidney are end-arteries, so that ligation of an accessory vessel involves the risk of impairing the blood supply to the corresponding portion of the kidney. This demarcation of the blood supply was clearly shown on radiographs taken after direct puncture of the main renal artery. The major portion of the kidney was outlined by contrast medium, but the inferior pole, which derived its blood supply directly from the aorta via an accessory vessel, was not outlined. *G. Ansell*

History of Medicine

563. **Pediculosis and Pulicosis in Art.** (Pediculosis und Pulicosis in der Kunst)
H. W. SIEMENS. *Hautarzt* [*Hautarzt*] **5**, 416–420, Sept., 1954. 13 figs., 3 refs.

In the Middle Ages and early modern times the process of removal of lice from the hair by means of the fingers, combs, or fine brushes has been a subject for many artists. One of the earliest examples, which is reproduced in this paper, is a woodcut of about 1480 in the Hortus Sanitatis collection (Fig. 1), in which a

FIG. 1

woman is seen brushing lice from the hair of a man into a bowl. The removal of lice was generally considered to be a normal part of a woman's domestic duties, and Malinowsky states that this is still the case in certain uncivilized tribes in New Guinea, removal of lice being one of the few intimate relationships between man and woman allowed to take place in public. The golden age of Dutch painting produced a number of domestic scenes portraying mothers removing lice from their children, outstanding amongst which is the picture called *Moeder Taak* ("Mother's Duty") by Pieter de Hoogh. In sharp contrast to the serenity of the Dutch domestic scene is the picture by Murillo depicting a street urchin being deloused while with one hand he clutches a loaf of bread and with the other holds off a dog.

Pictures dealing with fleas have a different character, portrayal of a routine domestic task giving place to the surprise, excitement, and fun of a good flea chase. A copper lithograph of the eighteenth century, for example, shows a disorderly scene as skirts are pulled up and clothing removed in an attempt to catch the quarry. Even to-day, when the psychology of humour has changed, the flea is still a source of fun, as is illustrated by the drawing (Fig. 2) by the famous Dutch cartoonist, Jo

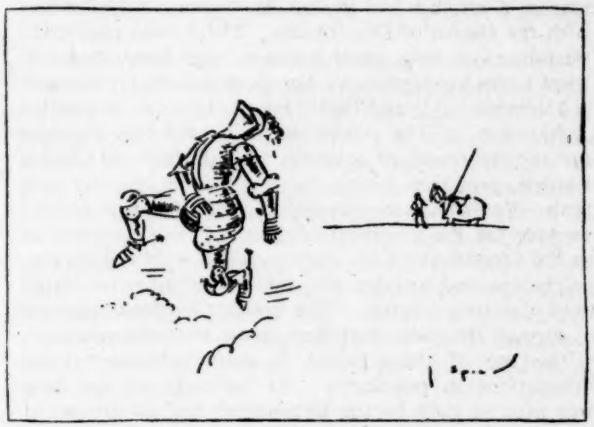

FIG. 2

Spier, entitled "A Knight of Drakenburg", portraying the disastrous effect on the knight's dignity of a flea at large beneath his armour. *Ruth Hodgkinson*

564. **History of the Use of Colchicum and Related Medicaments in Gout. With Suggestions for Further Research**
E. F. HARTUNG. *Annals of the Rheumatic Diseases* [*Ann. rheum. Dis.*] **13**, 190–200, Sept., 1954. 3 figs., bibliography.

The use of colchicum first as a poison and later in the treatment of gout can be traced back at least 2,000 years. The new hormones, cortisone and ACTH, have by no means usurped the ancient and useful position of this drug. The most important known effect of colchicum, which is to inhibit completion of mitosis or the division of cells, may or may not be related to its favourable effect on an acute attack of gout. Other theories as to its mode of action in gout have been proposed, but without sufficient evidence to establish their validity. The toxicology of colchicum is unique in that it produces its lethal effects slowly, requiring a number of hours to cause death in carnivora and longer in herbivora. Some poikilotherms are practically immune to its toxic effects, unless artificially heated.

Colchicum autumnale L., from which colchicum is obtained, is a perennial plant of the lily family, and must not be confused with the crocuses, which are of the iris family and contain no colchicum. It is probable that colchicum was known to the early Greeks under the term "Ephemeron, which some call Colchicon". It was first referred to, and as a poison, by Theophrastus, and subsequently by Dioscorides, from whose *Herbal*

two pictures of Ephemeron are reproduced. Alexander of Tralles (*c.* A.D. 550) in his *Therapeutica* made no mention of either ephemeron or colchicum, but recommended hermodactyl as the drug of choice. He gave no botanical description and the real identity of hermodactyl is in dispute. The reasons in favour of identifying hermodactyl with colchicum are: first, that the indications and effects appear similar; and second, that Alexander does not once mention colchicum or ephemeron, a notable fact in that he was naturally familiar with the *Herbal* of Dioscorides. The Arabic physicians introduced a new term, surugen, and later made all three terms synonymous. Serapion said that " Surugen is Hermodactyl " and that " Hermodactyl is also called Achimeron ". The Arabs recommended this Surugen for the treatment of arthritis. Meanwhile, in Central Europe, probably during the late Middle Ages, a new term—*Herbstzeitlose*—developed, and this was recommended for the treatment of gout. The controversy as to the identification of *Herbstzeitlose* with ephemeron, colchicum, and surugen, which immediately arose, lasted until the 19th century. The bulk of evidence appears to support the thesis that these terms are synonymous.

The use of these plants in gout underwent great fluctuations in popularity. As hermodactyl the drug was used in gout by the Byzantines, and as surugen it was used by the Arabs. As hermodactyl it appeared in the earliest English medical literature, and as *Herbstzeitlose* in that of Central Europe. By the 15th century, however, its use in gout had fallen into great disrepute, because of the secondary toxic manifestations which physicians had difficulty in controlling. As a result almost all the physicians of the 17th and 18th centuries ignored colchicum in the treatment of gout.

The modern history of the use of colchicum in gout starts with Nicolas Husson, not a physician but an officer in the French Army, who concocted a panacea called *eau médicinale*, the active ingredient of which was found to be colchicum. With the writings of Scudamore (1819) colchicum became the established treatment for acute attacks of gout. This opinion was supported by the elder Garrod, since whose time very little new has been learned about the administration or mode of action of the drug.

The effect of colchicum in arresting mitosis has been used experimentally in tumour research, starting with Dustin and his associates in 1933. This work has had profound significance in cancer research, as well as in many other fields, such as endocrinology, genetics, and cytology. A study of the history of colchicum brings to light many still unsolved problems related to its isolation, administration, and pharmacodynamics, and the metabolism and the mode of action of colchicum in gout is an open field for research.—[Author's summary.]

565. **Leonardo's Thoracopagus.** (Zum Thorakoparasiten Leonardos)
L. BELLONI. *Zentralblatt für allgemeine Pathologie und pathologische Anatomie* [*Zbl. allg. Path. path. Anat.*] **92**, 350–355, Oct. 25, 1954. 6 figs., 16 refs.

566. **The Embryology of Leonardo da Vinci.** (Die Embryologie Leonardos da Vinci)
H. BÖTTGER. *Centaurus* [*Centaurus (Kbh.)*] **3**, 222–235, 1954. 7 figs.

This paper sums up the work done by Leonardo da Vinci in the field of embryology, as a result of which he developed a knowledge of that subject which was far in advance of his time. Although da Vinci had contemplated a work on anatomy while engaged upon his gigantic equestrian statue of Francesco Sforza, Duke of Milan, in 1489, it was not until 1503 that he found leisure to pursue these studies in earnest—when, in fact, he was preparing the preliminary sketches for his " Battle of Anghiari ". He noted at the time that while he would need to dissect three cadavers for a full understanding of the working of the body, he would require a further three dissections of the female cadaver in order to penetrate the great mystery of the uterus and its fruit. The result of these observations are, for the most part, included in the so-called *Quaderni d'anatomia*, in which Leonardo reveals his tireless, probing intelligence in action; in concise, penetrating notes written in mirror-writing against the illustrations, he seems to hold converse with himself, establishing the true and demolishing the false conclusions which come into his mind, and broods over the internal bond linking the organisms of mother and child, the life drawn by the still sleeping child from the mother through the umbilical cord, and the common soul moving both. He throws fresh light upon the whole problem of generation as he takes up and examines traditional theories, resuscitates those that had been lost or forgotten, and submits them all to the discipline characteristic of the Renaissance—the unprejudiced investigation of Nature.

The progress of the illuminating thought of that great mind is set out in this article, illustrated with reproductions of Leonardo's own sketches. Perhaps the most striking quotation is da Vinci's prophetic note on inherited characteristics: " The blacks are not made so by the sun in Ethiopia: for if black parents conceive a child in Scythia it will also be black. A white woman made pregnant by a black will produce an ash-grey (*bigio*) child. This goes to show that the seed of the mother has an influence on the embryo equal to that of the father ". The laws which govern inheritance were not discovered for 300 years after da Vinci. Indeed, in da Vinci himself and in the unique conception of the world and of man which he gave to his age we may see the link between the old order and the new.

D. P. McDonald

567. **Manuscriptum Alberti Halleri ad historiam medicinae pertinens.** [In German]
E. HINTZSCHE. *Centaurus* [*Centaurus (Kbh.)*] **3**, 211–221, 1954. 2 figs., 16 refs.

The author discusses in some detail a manuscript of Albrecht von Haller which is concerned in part with medical history, and corrects certain erroneous impressions concerning it. For example, the manuscript in no way provides a systematic history of medicine, as suggested by Sudhoff and Fulton, but rather a bibliography,

arranged chronologically and under separate headings, of medicine and its ancillary sciences. Haller apparently started it while engaged upon his revised and greatly enlarged edition of Boerhaave's *Methodus discendi artem medicam*, which he published, under the title *Methodus studii medici, emaculata et accessionibus locupletata*, in 1751. This present manuscript does not contain Boerhaave's original text, but only the notes thereto which Haller compiled. To these he appears to have added, under the appropriate headings, all that he had ever read and extracted in the course of some 25 years' study. The resulting manuscript has 734 folio pages, few of which are left empty. For the student of medical history the most interesting sections are *De studio practico* and *De historia medicinae*, though Haller himself states specifically that he does not set out to write a history of medicine but only to give a list of writers from whom such a history could be composed. He brings to the task no fresh knowledge of his own.

A contemporary eulogy of Haller's labours is quoted. Haller marked with an asterisk the titles of all books which he had not read; nevertheless, it seems that he must have perused and abstracted in all some 6,000 volumes on medicine, surgery, anatomy, and other related subjects during the course of a long life largely occupied with other and more important matters. Castiglioni saw in the *Methodus studii medici* one of the first attempts at a systematic history of medicine, but while Haller certainly introduced a new outlook, the *Methodus* cannot be said to have played any great part in the advance in that field. *D. P. McDonald*

568. **Avicenna**

M. SANAI. *Lancet* [*Lancet*] **2**, 329–330, Aug. 14, 1954. 1 fig., 1 ref.

On April 29, 1954, in the presence of an international gathering of eminent medical men, scientists, and scholars, the Shah of Persia unveiled a mausoleum to the memory of Hussein, son of Abdullah Abu Ali ibn Sina, better known to the Western world as Avicenna, on the occasion of the millenary of that universal genius. The event took place at Hamadan in western Persia (the Ecbatana of Herodotus) where Avicenna died in A.D. 1037. According to Moslem reckoning, the millenary coincided with our year 1950, but its celebration had to be postponed for various reasons.

Born in A.D. 980 in north-east Persia, Avicenna—the name is perhaps a corruption of ibn Sina—grew up and was educated at Bokhara (now in the U.S.S.R.). By the age of 10 he had mastered the Arabic language and literature as well as that of Persian, his native tongue. Then applying himself to the study of jurisprudence, natural sciences, logic, and mathematics, he not only acquired a wide knowledge in these fields but made contributions to them. He then turned to medicine, and by the time he was 16 his reputation as a medical authority was widespread. After successfully treating the king's son he was given access to the magnificent library of the Samanide kings, and by the age of 18 he was reputed to have mastered all the available knowledge of his time. Avicenna's later life, spent in various Persian towns, was, like his learning, many-sided, and he was active as physician, teacher, author, and statesman. His writings, numbering about a hundred, were mainly in Arabic, as this language could be understood throughout Islam. Among his Persian works, however, his *Encyclopaedia of the Sciences* has been of particular importance as a source-book of Persian scientific terminology. His *Kitab al Shifa* and *Qanum* (*Canon of Medicine*, an immense work of about a million words) represent his *magna opera* in the realms of science and medicine.

Avicenna was the most outstanding representative of the golden age of Islamic learning, which extended from the 8th to the 12th century of our era. During this period the Moslems translated and enlarged Greek science and philosophy, although the acquaintance of Persians with Greek medicine and philosophy goes further back to the 5th century, when the university centre of Jundishapur in south-west Persia was founded and soon became a refuge for scholars banished from Edessa and Athens. In Europe Avicenna's reputation stood high. His *Qanum* was translated into Latin in the 12th century and remained a sort of " medical bible " for six centuries, parts of it still being taught in the universities of France until the 18th century. *H. P. Tait*

569. **Robert Burns and his Heart**

E. H. VINCENT. *Surgery, Gynecology and Obstetrics* [*Surg. Gynec. Obstet.*] **99**, 245–259, Aug., 1954. 5 refs.

Robert Burns, the eldest of the seven children of William Burnes [*sic*] and his wife, Agnes Broun, was born in January, 1759. Throughout his later childhood and adolescence the family went through difficult economic times; young Robert was assisting at the threshing when 13, and at 15 he was the principal labourer on the small family farm. During this period of overworked adolescence he suffered from numerous bouts of nervous depression, nocturnal headaches, and cardiac palpitation associated with feelings of faintness and suffocation. From this early strain he never really recovered, and in later life was seldom free from illness.

In 1784 Burns had a severe physical breakdown with alarming symptoms, and for this his physician, Dr. John Mackenzie of Mauchline, actually prescribed cold baths and continued farm work. During his visits to Edinburgh later on he had numerous riding accidents, and once was thrown from a coach and sustained a severely strained knee which laid him up for several weeks. This joint injury never healed satisfactorily in spite of the devoted ministrations of the celebrated Drs. James Gregory and Alexander (" Lang Sandy ") Wood of Edinburgh.

Leaving the capital, where he realized his dazzling popularity would not last, Burns in 1788 married Jean Armour and rented a small farm near Dumfries. At the same time he applied for a post with the Excise, hoping to combine the activities of farmer and exciseman. In spite of hard work the farm proved a failure, and in 1791, after ridding himself of the lease, Burns moved with his wife and family into Dumfries, where as exciseman his salary enabled them to live in some comfort. He did not

regard himself as an invalid, but as a result of his frequent feverish illnesses and numerous accidents his activities were limited and he rested a great deal. In 1795 he was seriously ill with an arthritis and fever which his physicians called "flying gout". For this he was recommended sea-bathing and country life, and so poor Burns betook himself to Brow on the Solway. Writing from there to a friend he describes himself as "pale, emaciated and so feeble as occasionally to need help from my chair—my spirits fled!" Returning shortly afterwards to Dumfries all the worse for his sea-bathing, he felt himself so near death that he wrote to his father-in-law asking Mrs. Armour to come immediately to look after Jean, who was expecting another child. Three days later, on July 21, 1796, Burns was dead.

The author of this article considers that there is no evidence to support the assertion of Dr. Currie, the poet's first biographer, that Burns died from alcoholic excess and venereal disease; rather is the evidence in favour of the diagnosis of rheumatic endocarditis, as suggested by the late Sir James Crichton-Browne and others.

H. P. Tait

570. **The Viper Soup Dear to Mme de Sévigné and Mme de Lafayette.** (Le bouillon de vipères cher à Mme de Sévigné et à Mme de Lafayette)
B. LYONNET. *Lyon Médical* [*Lyon méd.*] **192**, 62–66, July 18, 1954. 5 refs.

The use of the viper or its extracts in therapeutics dates from antiquity. It is believed to have been introduced into the formulary by Mithridates or, according to some, by Andromache of Crete, physician to the Emperor Nero; its virtues were extolled by Galen, and it was used by the Roman Emperors Antony and Marcus Aurelius. In the ruins of Pompeii there stands to this day the remains of a pharmacy on the front of which is a symbol consisting of two intertwined vipers.

In this short review of the subject the author quotes from letters written by Mme de Sévigné, who in 1679 described to her daughter the wonderful effect of soup made from vipers on her friend Mme de Lafayette, who became "visibly stronger every day" as a result. In another letter to her daughter she gives the following recipe: "each morning take two vipers, cut off their heads, skin them, cut them into pieces, and stuff them into a chicken". She herself claimed that her good health was due to this preparation, which "purifies, soothes, and refreshes the blood". Other quotations, from an erudite work by Chaumartin of Vienne, show that it was believed that the viper was a panacea that would cure chicken-pox, rheumatism, ulcers, and various skin diseases. The fat of the viper was an aphrodisiac, its dried liver stimulated uterine contractions, and the dried head hung round the neck of a child would prevent convulsions.

Preparations which contained viper as a constituent were for long used in France, and it was still actually included in the French pharmaceutical codex as late as 1908. In the Musée des Hospices Civils in Lyons stands an enormous vase of pewter and bronze dating from the 17th century which was formerly used to store a mixture containing dried viper as one of its constituents. This mixture, which included seventy-one other ingredients, was annually prepared publicly and with great ceremony by the Master Apothecary himself.

The author concludes that although almost certainly extract of viper had no pharmaceutical action, it is not impossible to imagine that pharmacological science may yet produce some active and useful substance from it. He introduces his paper, however, with a quotation from the wise Montaigne: "Telles autres singeries qui ont plus le visage d'un enchantement magicien que de science solide".

F. Clifford Rose

571. **How a King of France was Cared for: the Medical Service of Louis XIV.** (Comment était soigné un roi de France: le service médical de Louis XIV)
R. VAULTIER. *Presse médicale* [*Presse méd.*] **62**, 1320–1323, Sept. 29, 1954. 8 figs.

The intimate and precise details of the habits and illnesses of King Louis XIV of France can be studied in the diaries and notebooks of his doctors, which are preserved in the Bibliothèque Nationale. The royal medical service consisted of eight physicians, eight surgeons (two of whom always accompanied the king when out hunting), dentists, apothecaries, four assistants, two distillers, and a herbalist.

As a child he suffered from the common ailments—measles, chicken-pox, and scarlet fever—and later from typhus, which he caught while visiting military camps. His chief physician, Vallot, used to record day by day the complaints of the young sovereign, and he knew that these were read by the Queen Mother; when, therefore, the king suffered from an attack of gonorrhoea—*ce coup de pied de Vénus*—the physician merely wrote that there was "a congenital weakness and the King should not do too much riding or vaulting"; he was treated with injections of succinic acid, and the discharge soon stopped.

The king, as had his father and grandfather, suffered much from gout which was aggravated by his gargantuan meals (although he was sparing of wine) and this probably hastened his death, which was, however, mainly due to senile gangrene and chronic nephritis. At lunch the king demolished the best part of three chickens, apart from soup, entrées, and other courses, and when Dr. Fagon, the first physician, complained to the chief *maître d'hôtel* about the size of the meals he was told haughtily "it is for us to make the King eat and for you to purge him", and indeed the royal purge took place with great ceremony. Once each month the king stayed in bed for mass and two hours later was given a mixture of senna and rhubarb; it was considered a great honour to give the king the bedpan, and the senior physician examined the results carefully and made detailed notes. A typical day in the king's life is recounted, and the elaborate etiquette which governed his every act is described in detail.

The author concludes that the only legitimate criticism that can be made of the king's devoted and reasonably competent doctors is that they applied the therapeutic methods then in vogue with too much zeal.

F. Clifford Rose